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The Effects of Lowering Cholesterol on Vasodilation

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THE EFFECTS OF LOWERING CHOLESTEROL ON VASODILATION

by

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Each person whose signature appears below certifies that this dissertation in his/her opinion, is adequate in scope and quality as a dissertation for the degree of Doctor of Public health.

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ABSTRACT OF THE DISSERTATION

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Endothelial dysfunction has been found prior to any signs of atherosclerotic plaque formation in patients with a variety of risk factors for atherosclerosis. Elevated serum cholesterol has repeatedly been associated with endothelial dysfunction as demonstrated by impaired vasoreactivity to vasodilating stimuli.

The aim of this research was to determine whether short term lowering of serum cholesterol levels by life style changes or by cholesterol lowering medication could reverse or reduce the endothelial dysfunction. The brachial artery diameter was measured by high-resolution ultrasound at rest and during reactive hyperemia pre and post-intervention. Fifty-three subjects with cholesterol levels above 240 mg/dl were randomly assigned to three groups: Lifestyle change (n=17), medication (n=17), and placebo (n=19).

All individuals were assessed for readiness to change using Prochaska's and DiClemente's stages of change. All individuals were the highest in contemplation stage at the beginning of the intervention. Only individuals in the lifestyle group moved to the

action stage of change after intervention. There was no change in the individuals' reported mood state pre and post-intervention.

No correlation was seen between the lipid values and the brachial artery diameter change following the six week intervention period for any of the groups and groups did not differ on reactivity to vasodilating stimuli pre or post intervention. There was a statistically significant drop in both the total cholesterol and LDL-cholesterol in the lifestyle and medication groups, but no change in the HDL-cholesterol in all three groups. This contradicts previous research showing that HDL-cholesterol levels decrease with low fat diet.

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Acknowledgments

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CHAPTER 1

INTRODUCTION

Definition of the Problem

Total serum cholesterol below 200 mg/dl is regarded as desirable by the National Heart, Lung, and Blood Institute (NHLBI, 1985), yet the mean cholesterol level for Americans is 213 mg/dl (NCHS, 1986). It is estimated that about 60 million adults have blood cholesterol levels that place them at high risk for atherosclerotic heart disease (ASHD) (Sempos, 1989). Serum cholesterol levels below 200 mg/dl are classified as "desirable blood cholesterol" between 200-239 mg/dl as "borderline-high blood cholesterol" and above 240 mg/dl as "high blood cholesterol" (NCEP, 1988 & 1993). The cut point of 240 mg/dl that defines high cholesterol is a value above which risk of coronary heart disease (CHD) rises steeply, and corresponds approximately to the 75th percentile of the adult US population (NCEP, 1988 & 1993). Serum low density lipoprotein cholesterol (LDL) level below 130 mg/dl is considered "desirable LDL-cholesterol", 130-159 mg/dl are considered as "borderline high risk LDL cholesterol, and LDL levels of 160 or greater are "classified as high risk LDL-cholesterol" (NCEP, 1988 & 1993). The Coronary Prevention Trial showed that men at high risk were able to reduce ASHD by 2% for every one percent decrease in blood cholesterol levels (LRCP, 1984).

High cholesterol levels have also been shown to effect the endothelial function of the blood vessel wall before there are any signs of atherosclerosis, and independently of other risk factors for heart disease. High cholesterol levels effect the function of the

endothelium-derived relaxing factor (EDRF) that causes vasodilation but the exact mechanism has not yet been identified. Cholesterol may impair synthesis or release of EDRF or it may impair it's transport and function.

The impairment of EDRF by high cholesterol levels in animals and humans is well documented in the literature (Chowienczyk et al, 1992; Creager et al, 1990, 1992; Bialecki & Tulenko, 1993; Lerman et al, 1993; Bedarita et al, 1993; Simonet et al, 1992; Pomerantz et al, 1993; Girerd et al, 1990; Mugge et al, 1991; Shepherd et al, 1991). There are however few resent reports that show that the endothelial dysfunction caused by high cholesterol is reversible in the coronary arteries when serum cholesterol levels are reduced (Leung et al, 1993; Egashira et al, 1994; Treasure et al, 1995). What has not been demonstrated is whether this impairment in the vessels of the extremities is permanent or if it is reversible with a decrease in blood cholesterol. The hypothesis of this research is that impaired vasodilation in the brachial artery will improve or normalize with a decrease in blood cholesterol level and therefore arterial responsiveness to vasodilating stimuli will improve. The cholesterol level will be reduced by lifestyle changes in one group and by cholesterol lowering medication in another group.

Significance of the Research

It is of special interest to determine if lowering cholesterol levels by lifestyle change or cholesterol lowering medication can produce a reversal effect of the impaired vasodilation in the brachial artery. This concept has not been previously tested. In previous studies both diet and medications have been used synergistically to lower the cholesterol. It is also of a great importance to compare the findings to determine whether

there is any difference between the effects of lowering cholesterol by lifestyle changes or by the use of medications. It is in the professional and public interest to confirm if early treatment of hypercholesteremia prevents or reverses abnormal vasodilation responses and thus lowers the risk of atherosclerotic heart disease.

Research Questions

1. Will lowering the blood cholesterol level by lifestyle modifications or through medication reverse the abnormal Brachial artery response response to vasodilating stimuli such as post occlusion hyperemia in the brachial artery?

2. Is it possible to significantly lower serum cholesterol in outpatients through lifestyle changes?

3. Is there any difference in the mood of the individuals who lower their cholesterol level by medication as compared to those who lower their cholesterol level by lifestyle change?

4. Are the individuals who are at the action stage of change in the Transtheoretical model at the beginning of the intervention more likely to succeed in lowering their cholesterol regardless of the group in which they are randomized?

Definitions

Angina Pectoris: A diagnosis applied to patients complaining of chest pain induced by myocardial ischemia.

Atheroma: A mass of plaque of degenerated, thickened arterial intima occuring in atherosclerosis.

Atherosclerosis: Deposits of yellow plaques (atheromas) containing cholesterol, lipoid material, and lipophages are formed within the intima and inner media of large and medium arteries.

EDRF: Endothelial-Derived Relaxing Factor, a substance released by the endothelium that causes vasodilation.

Endothelium: A layer of endothelial cells that covers the inner wall of the blood vessels.

Intima: A general term denoting an innermost structure.

Myocardial ischemia: Deficiency of blood supply to the heart muscle due to functional constriction or actual obstruction of the coronary arteries.

Vasodilation: A state of increased caliber of the blood vessels.

Vasoconstriction: The diminution of the caliber of vessels, especially constriction of arteriols leading to decreased blood flow to a part.

CHAPTER 2

LITERATURE REVIEW

Introduction and Overview

Coronary heart disease (CHD) is the major cause of death in the United States and other industrialized countries. It accounts for more deaths annually than any other disease, including all forms of cancer combined (NCEP, 1984 & 1993). Coronary artery disease is not only the principal cause of death in this country, but it is also responsible for significant morbitity. Angina pectoris is a diagnosis applied to patients complaining of chest pain induced by myocardial ischemia. The mechanism is basically related to an inbalance between coronary blood supply and myocardial demand. Coronary artery flow may be limited by progressive endothelial plaque formation resulting in fixed obstruction to coronary blood flow. Coronary artery vasoreactivity (constiction and dilation) to various stimuli may also significanly effect coronary blood flow.

Reports of dramatic subjective improvement in frequency of angina pectoris, and frequent anectotal reports of improvement in exercise tolerance, after just few weeks of intensive lipid lowering therapy have been reported by a variety of lifestyle modification programs. Dr. Dean Ornish reported 90% reduction in angina episodes in the intervention group compared with the control group, but only minimal reversal in coronary artery stenosis by angiographic follow up. The improvement in symptoms have been reported to occure within 3-5 weeks of initiation of therapy, and are thus clearly not related to reversal of the fixed atherosclerotic obstructive lesions.

Studies have been done to assess the vasoreactivity, and results are clear and consistent

that there is an impairement of the endothelial vasodilation in the presence of certain risk factors for coronary heart disease. Reduction of elevated serum cholesterol is accepted as one of the major factors in reducing the risk of death from CHD (McDougall et al, 1995). High serum cholesterol is not only a major risk factor for CHD but also appears to impair the endothelial function of the vessels before any atherosclerotic signs are evident (Celermajor et al, 1992).

The endothelium covers the inner surface of all blood vessels and provides a smooth, almost friction-free internal surface, permitting the free flow of blood. Endothelial cells have been recognized as playing a major role in modulating vascular smooth muscle tone by synthesizing and metabolizing vasoactive substances such as endothelial-derived relaxing factor (EDRF) (Vanhoutte et al, 1994). Elevated serum cholesterol causes impairment of the function of EDRF (Pearson et al, 1990). It is estimated that more than 60 million adults in the United States have cholesterol levels above 240 mg/dl (Sempos, 1989) which have been shown to effect the endothelial function of the blood vessel wall before there are any signs of atherosclerotic heart disease (ASHD) (Creager et al, 1990).

Some studies have shown that the endothelial dysfunction caused by high cholesterol is reversible in the coronary arteries when serum cholesterol levels are reduced (Leung et al, 1993). No studies have been done to show the effects of lowering cholesterol on endothelial function of the brachial arteries. However there is one study that showed that the endothelial function in the brachial arteries improved with smoking cessation (Celermajor et al, 1990).

Hypercholesterolemia is usually treated with lifestyle changes and cholesterol lowering medications. Cholesterol lowering medications are very successful in lowering the cholesterol however there are some adverse effects (PDR, 1995). Some of the adverse effects are mild liver disease, muscle crumps, dizziness and alterations of taste. Therefore they are only recommended for individuals that maintain high cholesterol in spite dietary therapy (NCEP, 1988 & 1993).

Dietary treatment has been shown to be effective on lowering the total cholesterol and LDL-cholesterol on an inpatient basis, but it has not been as successful with the outpatient (Dishman, 1988; Wadden and Bell, 1990; Rossi et al, 1990). Also the dietary treatments tend to lower the HDL-cholesterol. HDL-cholesterol is considered to have a protective effect against CHD. The dietary treatments put the effort on the nutritional and exercise recommendations but have not been based on a systematic behavioral model. The Transtheoretical model postulates that the cessation of a behavior and the acquisition of another involves a progression through five stages of change, precontemplation, contemplation, preparation, action and maintenance (Prochaska and DiClemente, 1992). This model can be used in developing lifestyle change programs for lowering cholesterol.

This literature review will discuss the EDRF and it's function, it's relationship to serum cholesterol and the effects of lowering serum cholesterol on the vasodilation. It will also discuss the treatment of serum cholesterol by cholesterol lowering medications and by lifestyle changes. The transtheoretical model will be explained as a possible theoretical model that if applied in lifestyle programs may increase the programs' success rate.

Endothelial-Derived Relaxing Factor

More than 20 years ago, vascular scientists observed that vasodilation was dependent on the presence of an intact, healthy endothelium (Furchgott and Zwadzki, 1980). The endothelium covers the inner surface of all blood vessels and provides a smooth, almost friction-free internal surface, permitting the free flow of blood. Endothelial cells have been recognized as playing a major role in modulating vascular smooth muscle tone by synthesizing and metabolizing vasoactive substances such as endothelial-derived relaxing factor (EDRF) (Vanhoutte et al, 1994). Pearson et al, (1990), identified certain conditions that cause impairment to the function of EDRF. These conditions are: smoking, stress, diabetes, hypertension and hypercholesterolemia.

After an extensive study, Palmer et al (1987) demonstrated that EDRF shared many properties with nitric oxide and may in fact be the same. This led to the recognition that endothelial cells produce nitric oxide from L-arginine via the action of nitric oxide synthase. Thus L-arginine is the precursor for the synthesis of nitric oxide which most scientists now believe to be identical with EDRF (Girerd et al, 1990). The recognition `of L-arginine as the precursor to EDRF has let to many studies concerning the nature and function of EDRF (Mugge et al, 1991). EDRF has a half life of few seconds therefore it has not been possible to measure directly. The effects of EDRF are seen by measuring parameters such as arterial blood flow velocity and arterial diameter after vasodilation is induced by vasodilating agents, such as acetylcholine and induced active hyperemia (Celemajor et al, 1992). EDRF is a potent vasodilator that not only controls the tone of

the underlying smooth muscle cells in the vessel wall, but also inhibits platelet adhesion and aggregation, monocyte adherence and chemotaxis (Vanhoutte et al, 1994).

Experiments by Cohen et al (1989) demonstrated that two substances play a predominant role in the release of EDRF. These are serotonin and adenosine diphosphate (ADP). Activation of either receptor elicited release of nitric oxide. However the signal transduction mechanism of the two receptors on the endothelium is different. Experiments of the effect of the intact endothelium on the aggregating platelets illustrate the fundamentally important role of the endothelium. Theoretically, circulating platelets should not undergo aggregation in a normal blood vessel with an intact endothelium. However aggregation may be initiated under conditions of stress such as elevated blood pressure that in turn leads to increased shear forces within the vessels. This results in the release of serotonin, ADP, and thrombin. In combination, these factors will act upon the endothelium to cause a massive release of EDRF and the subsequent relaxation of the smooth muscle cell layers. The blood vessels will dilate, and this will have the beneficial effect of flushing out the developing thrombus (Cohen et al, 1989).

Endothelial Dysfunction

The mechanism of vasodilation via EDRF release does not work efficiently when there is a dysfunction in the endothelium. Potential mechanisms to explain this phenomenon include impaired synthesis or release of EDRF, the presence of functional or mechanical barriers that limit transport of EDRF from the endothelium to the vascular smooth muscle, inability of the vascular smooth muscle to relax in response to EDRF, and competitive vasoconstrictive stimuli (Girerd et al, 1990). It is unlikely that a

mechanical barrier explains this phenomenon, because morphological lesions do not develop in the endothelium of the microvasculature (Osborne et al, 1989). Bioassay experiments, however, have suggested that impaired synthesis or release of EDRF might contribute to this blunted relaxation of the vessels (Shimokawa et al, 1989; Verbeuren et al, 1987). Girerd et al (1990) tried to identify the possible mechanism of the EDRF dysfunction. Their study results have shown that in hypercholesterolemic rabbits , endothelium-dependent vasodilation may be normalized acutely by administration of L-arginine, the precursor of EDRF, which may indicate that the probable mechanism for the dysfunction is impairment in the synthesis of EDRF.

Pearson et al (1990) identified certain conditions that exacerbate the pathogenic processes. These conditions or risk factors are smoking, cholesterol rich dietary intake, age, high blood pressure, stress and diabetes.

EDRF and Cholesterol

Studies in animals and humans with atherosclerosis have demonstrated abnormalities in vascular function. Impaired endothelium dependent vasodilation, altered smooth muscle relaxation and potentiated vasoconstriction to a variety of agonists have been observed (Creager et al, 1990). Hypercholesterolemia in non atherosclerotic individuals may decrease synthesis, release or transport of EDRF, or alter the ability of the vascular muscle to respond to vasoactive substances (Creager et al, 1990) . Girerd et al (1990) also demonstrated that hypercholesteremia possibly interferes with the synthesis of L-arginine in humans. This was done by administering L-arginine intravenously to hypercholesterolemic individuals and individuals with normal

cholesterol levels. They observed that the intravenous administration of L-arginine improved the endothelium dependent vasodilation in the hypercholesteremic individuals but not individuals with normal cholesterol levels. Casino et al (1993) demonstrated that the endothelial dysfunction could be a consequence of reduced bio-availability of nitric oxide whose precursor is L-arginine.

Hypercholesteremia causes vessels to be resistant to factors (such as vasodilating drugs) that cause vasodilation by stimulating the release of EDRF. Creager et al (1990), demonstrated that vasodilation in response to methacholine chloride (a vasodilating agent that stimulates the release of EDRF) is blunted in hypercholesteremic humans. Creager et al (1992) also demonstrated that hypercholesterolemia in the absence of atherosclerosis is associated with impaired smooth muscle vasodilation. The basal blood flow and vascular resistance in normal and hypercholesterolemic subjects before and after methacholine and nitroprusside injection were measured using a calibrated mercury-in-silastic strain gauges. Nitroprusside is a vasodilating agent that stimulates the smooth muscle of the vessels directly and methacholine chloride stimulates the EDRF. The cholinergic vasodilation was significantly attenuated in the hypercholesterolemic patients in comparison to normal subjects after methacholine was infused in the artery. However there was no significant difference when nitroprusside was infused. These results not only suggest that hypercholesterolemia impairs the effect of EDRF on vasodilation but also imply that the defect is reversible.

Celermajer et al (1993) used the same methods as those used in my study, to show that the vasodilation of the brachial artery is impaired in smokers. Cigarette smoking is a

major risk factor for atherosclerosis and is strongly associated with coronary, cerebral and peripheral vascular disease (DHHS, 1983; Holbrook et al, 1984). The brachial artery was chosen for several reasons. First, the incidence of atherosclerosis is low on the upper extremity (Creager et al, 1990). Second, unlike the walls of the larger arteries, the walls of the brachial artery do not develop atheroma after exposure to high levels of cholesterol (Juergens et al, 1980). Since the arteries on the upper extremities are not likely to have atherosclerosis or atheroma, the changes that can be seen will be due to the endothelial function. Celermajer et all (1993) measured the arterial diameter and the arterial blood flow velocity at rest and after inducing hyperaemia by inflation of a pneumatic tourniquet placed around the arm to a pressure of 300 mm Hg for 4.5 min, followed by release. They also took the same measurements after applying sublingual glycerine trinitrate (GTN) to induce dilation. In arteries lined with healthy endothelium, increased flow causes dilation of the vessels (Lauren, 1990; Rubanyi, 1986). This mechanism fails with endothelial dysfunction (Pohl, 1986; Young, 1987). In a study by Celemajor at al (1993), the endothelium-dependent (flow mediated) dilation was significantly impaired in the group of smokers as compared with control subjects. Also the ratio of flow-mediated to GTN-induced dilation was significantly impaired. In arteries lined with healthy endothelium, increased flow causes dilation of the vessels via release of EDRF. By contrast GTN causes vasodilation by direct action on the smooth muscle: its effect is therefore independent of the endothelium. This method was used to find out whether endothelial dysfunction is present in subjects at high risk for atherosclerosis before clinical evidence of vascular disease (Celermajer et al, 1992).

Zeiher et al (1993), demonstrated that vasodilator response of the coronary microcirculation to acetylcholine (a vasodilating agent that stimulates EDRF release) was blunted in patients with hypercholesteremia. This effect is apparently caused because of endothelial dysfunction and not because of smooth muscle dysfunction. When papaverine, a smooth muscle relaxant, was injected into the arteries, no difference in the vasodilation was found between the control group (normal cholesterol) and the hypercholesteremic group (Zeiher, 1993).

Endothelial Function Improvement

Many studies have been done on animals as well as on humans to demonstrate the effects of hypercholesteremia on the EDRF (Russell, 1993; Keaney, 1994; Cook, 1992; Girerd et al, 1990; Mugge et al, 1991). The results have been consistent. Serum total cholesterol levels above 240 mg/dl and LDL-cholesterol above 160 mg/dl cause impairment of the function of EDRF. However, the question that remains to be answered is whether the effect of high cholesterol on the EDRF can be reversed and how quickly the change can be demonstrated. To date there are very few studies that demonstrated that a reduction of serum cholesterol level leads to improvement of endothelial function of the coronary arteries in patients with hypercholesteremia and apparently normal coronary arteries (Leung et al, 1993; Egashira et al 1994; Treasure et al, 1995). The procedures used by Leung were very invasive (cardiac catheterization and coronary arteriography). These procedures are not risk free, and they are generally performed on patients who are symptomatic for coronary heart disease and have significant risk factors (Harrison's Principles of Internal Medicine, 1995).

Acetylcholine is known to induce vasodilation by stimulating EDRF. Leung et al (1993) has done research showing that the effect of acetylcholine is impaired by the presence of high cholesterol levels. Acetylcholine and several other factors induce vasodilation by stimulating the release of EDRF. In their study Leung et al (1993) demonstrated that the effect of acetylcholine was improved after cholesterol level were reduced by dietary changes and medications.

The population in Leung's el al (1993) study was 25 men with no angiographically evident atherosclerosis, whose mean age was 51 years (range 35-65). The mean total serum cholesterol concentration at base line was 274 mg/dl which was significantly reduced by 28.7%, to 197 mg/dl at follow up (six months later). The mean low density lipoprotein (LDL) concentration at base line was 220 mg/dl which was reduced by 35.6% to 143 mg/dl at follow up. The mean total cholesterol to high density lipoprotein (HDL) ratio at base line was 6.9 which was significantly reduced by 29.4% to 4.9 at follow up. No significant changes occured in the mean HDL and triglyceride concentration. Leung (1993) found that stimulation of vessels with acetylcholine at base line (when total cholesterol and LDL levels were high) had no effect on the vasodilation. However at the end of the study when the total cholesterol and LDL were reduced there was a significant change in the vasodilation. This observation suggests that there may be a threshold level of serum cholesterol at which endothelial dysfunction develops and at which level improvement of vasodilation may take place.

Several clinical trials have shown that angiographically detected atherosclerosis can regress with risk factor reduction, or lifestyle changes, especially diet restrictions and

cholesterol lowering therapy (Waters et al, 1991; Ornish et al, 1990). However the reduction is very modest and not sufficient to account for the dramatic change in reported episodes of angina pectoris (Treasure et al, 1995). The concept of recovery of the impaired ability of the coronary arteries to respond to vasodilating stimuli may therefore be a key to explain the dramatic improvement in symptoms despite the very modest reversed luminal diameter stenosis. Leung's et al (1993) study provided additional important data that endothelial dysfunction associated with hypercholesterolemia may be reversible with cholesterol reduction in man, even before the presence of angiographic evidence for atherosclerosis. Therefore early detection of hypercholesterolemia and its correction may improve the vasodilation and prevent the future development of atherosclerosis.

Egashira et al (1994) have also shown results similar to Leung et al (1993). In this study there were 9 participants in the intervention group and 7 in the control group who had single-vessel coronary artery stenosis (>75%) in one coronary artery and mild stenosis (<40%)in the other coronary vessels. The mean total cholesterol level for the intervention group was 272 +/-16 mg/dl and LDL was 195+/-25 mg/dl. After taking Pravastatin for six months the total cholesterol was reduced to 187+/-16 mg/dl and LDL to 120+/-12 mg/dl (cholesterol reduction was 31% and LDL reduction was 38%). Acetylcholine was used as the vasodilating stimuli. The coronary arteries were used for the arterial measurements. Significant differences were found between the hypercholesteremic group and the control group and the results agreed with Leung's et al (1993) conclusions.

Treasure et al (1995) have demonstrated that short term aggressive lipid-lowering therapy (40 mg of Lovastatin twice daily) for 12 days did not significantly improve the coronary artery endothelial responses to acetylcholine, even though the total cholesterol and LDL cholesterol levels were significantly reduced. The total cholesterol level dropped from 230 mg/dl to 145 mg/dl and the LDL cholesterol from 148 mg/dl to 99 mg/dl. There was no significant change in the HDL level. However longer-term lipid lowering therapy (5½ months) significantly improved epicardial coronary artery responses to acetylcholine. The total cholesterol after 5½ months of cholesterol lowering therapy with 40 mg of Lovastatin twice daily was 158 mg/dl, the LDL was 110 mg/dl and no significant changes in HDL. Treasure et al (1995) showed that lipid lowering had no effect in the short term but it improved coronary endothelial function in the long term in patients with symptomatic atherosclerotic coronary artery disease.

The evidence is clear that there are many benefits to lowering serum cholesterol. the research cited above shows that lowering serum cholesterol will improve the function of EDRF of the coronary artery endothelium and prevent atherosclerosis. A logical question to ask then would be how can cholesterol be lowered and this is the focus of the following section.

Treatment of Hyperlipidemia

The specific goal of cholesterol treatment is to lower the LDL-cholesterol to levels below the cut points for high risk (below 160 mg/dl) for those without any other risk factors for CHD or below 130 mg/dl if definite CHD or two other risk factors for CHD are present (NCEP, 1988 & 1993). There are two approaches to treatment: lifestyle

management and drug treatment.

Drug therapy. Drug therapy is considered for adults that, in spite of dietary therapy, still have an LDL-cholesterol level of 190 mg/dl or higher, and have no definite CHD or two or more other rick factors for CHD. If the patient has definite CHD or two other risk factors for CHD, the drug therapy should be considered at LDL-cholesterol level of 160 mg/dl or higher (NCEP, 1988). The goals of drug treatment are the same as diet therapy (NCEP, 1988 & 1993). The drugs of first choice are the bile acid sequestrants (cholestyramine, cholestipol) and nicotinic acid. Both drugs have been shown to lower CHD in clinical trials and their long term safety has been established (NCEP, 1988). Side effects of these drugs are abdominal pain, gastrointestinal problems (constipation, diarrhea, flatulence and nausea) and headache (PDR, 1995) The next pharmacãlogical consideration is the HMG CoA reductase inhibitors (lovastatin, Pravastatin). These drugs are very effective in lowering the LDL-cholesterol but their effects on CHD incidence has not been established (NCEP, 1988). The adverse effects of the HMG CoA reductase inhibitors are mild and transient. One percent of the patients taking HMG CoA reductase inhibitors experience some adverse effect (PDR, 1995). The adverse effects are: mild liver disease, muscle cramps, myalgia, myopathy, rhaptomyolysis (lyse of the muscle cells), alterations of taste, impairment of extra-ocular movement, tremor dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, anxiety, insomnia, depression and some others that are very rarely seen (PDR, 1995). The lipid profile should be checked in 4-6 weeks and in three months after the cholesterol lowering drug therapy begins (NCEP, 1988: PDR, 1995). The dosage of drug varies. For

the HMG CoA reductase 20-40 mg per days is the most common dosage, the expected LDL-cholesterol reduction is 25-35% and HDL-cholesterol is expected to increase by 5-10%. No CAD risk reduction and no long term safety have been documented.

Other drugs, such bile acid sequestrants and nicotinic acid, are expected to cause a 10-20% decrease in LDL-cholesterol and a 15-20% increase in HDL-cholesterol. The patient's acceptance of niacin (nicotinic acid) and compliance is poor. The side effects of niacin are flushing, itching, gastritis, hepatoxicity, hyperuricemia, and hyperglycemia (PDR, 1995; Brown et al, 1990). If the drug treatment is not successful the drug dosage is increased or a different drug is subscribed. Drug therapy is likely to continue for life. Hence the decision to use cholesterol lowering drug therapy should be made only after vigorous efforts at dietary treatment have not proven sufficient (NCEP, 1988 & 1993).

Lifestyle management. Diet is the main environmental determinant of plasma lipid concentrations, and dietary modification is recognized to be the first line of treatment for hyperlipidemia (Watts et al, 1992). The general aim of dietary treatment is to reduce elevated cholesterol levels while maintaining a nutritionally adequate eating pattern. The NCEP (1988 & 1993), recommends the Step-One and Step-Two Diets. The Step-One Diet consists of an intake of total fat less than 30% of the daily caloric intake, saturated fat less than 10% and total cholesterol less that 300 mg/day. The Step-Two Diet consists of total fat intake of less than 30% of the daily caloric intake , saturated fat less than 7% and cholesterol intake less than 200 mg/day (NCEP, 1988 & 1993). The Step-One Diet is easily achieved by reducing the major and obvious sources of fat and cholesterol in the diet. This can be achieved without a radical alteration in the diet. The Step-Two Diet

requires careful attention to the whole diet in order to reduce the saturated fat and cholesterol without reducing the intake of the necessary nutrients. The NCEP (1988) recommends that the cholesterol level as well as the adherence to the diet should be measured in 4-6 weeks after the dietary changes are begun.

Ornish et al (1990) used a very restrictive diet on individuals with CHD to assess whether patients outside the hospital can be motivated to make and sustain comprehensive lifestyle changes and, if so, whether regression of coronary atherosclerosis can occur as a result of lifestyle changes. However, these patients had one week of inpatient training and met twice a week, for four hours. Their diet contain 15-20% of the daily caloric intake as protein, 10% fat, (polyunsaturated/saturate ratio grater than 1), and 70-75% carbohydrates (predominantly complex carbohydrates). Cholesterol intake was limited to 5 mg/day or less. In addition to diet a stress management and exercise program was implemented. The total cholesterol fell by 24.3%, LDL-cholesterol by 37.4% and there was no change in HDL-cholesterol in 12 months.

McDougall et al (1995) studied the effects of a very strict vegetarian diet on 500 inpatient hypercholesterolemic adults. The diet contain 5% fat, 12% protein, 83% carbohydrates, and 60 g/day fiber. Exercise and stress management were also implemented. The study was only for 12 days. The total cholesterol was decreased by 11%, the HDL-cholesterol decreased 19%, the systolic blood pressure fell 7% and the diastolic blood pressure fell 5%. Bernard et al (1989) reported that a very low fat non-vegetarian diet, when fed to inpatients at the Pritikin Longevity Center, resulted in 23% reduction of total cholesterol and 16% reduction in HDL-cholesterol in three weeks.

Ornish et al (1983) reduced the total cholesterol over a period of 20 days by 20% but the HDL-cholesterol was also reduced by 17%.

Very little is known about the psychosocial effects of a lifestyle change program on the participants. The few studies available were focussed on patients that had a myocardial infarction and were participating in a rehabilitation program. The main lifestyle change that was considered was the exercise. Exercise was the target behavior because some studies have shown that exercise promotes improved mood (Blumenthal et al, 1982; Goff et al, 1985) and it increases self concept (Hilyer et al, 1979; McGowan et al, 1974). However resent studies showed that patients that participated in rehabilitation programs after an MI have not experienced a significant improvement in their psychosocial functioning in six months of participation in the program (Blumenthal et al, 1988). Many patients informally reported that they felt better after exercise but the psychometric measures did not show any evidence of improvement (Blumenthal et al, 1988; Erdman et al, 1986; Dracup et al 1991). Heller et al (1993) reported that intervention programs for post MI patients appear to improve quality of life. However they did not use standardized instruments for measuring the psychosocial function of the individuals. The questionnaire used by Heller et al (1993) provided only subjective assessment

Efficacy of dietary treatment. Several studies have been done to determine the efficacy of dietary treatment of hyperlipidemia. The results are varied, sometimes contradicting each other. Watts et al (1992) used a diet on outpatients consisting of 27% fat of the daily dietary intake, saturated fat was 8-10%, dietary cholesterol 100

mg/1000kcal, and dietary fiber 3.6 gm/1000kcal. Individuals were randomly assigned to three groups. The diet group was on the above diet. The diet plus Cholestyramin group, were on the same diet plus 8 mg of Cholestyramin and the usual care group, followed the advise of their regular physician. Patients' blood lipid profiles were tested every three months for three years. The diet group was able to lower and maintain a 14.2% decrease in total cholesterol, a 16.2% decrease in the LDL-cholesterol, 15.6% decrease in the cholesterol/HDL ratio and 20% decrease in triglycerides. The diet plus Cholestyramin group were able to reduce and maintain a 25.3% decrease in total cholesterol level, a 35.7% decrease in LDL-cholesterol, a 24.1% decrease in cholesterol/HDL ratio and no significant change in triglyceride levels (Watts et al, 1992).

Another study by Hunninghake et al (1993) showed that outpatients on the NCEP Step 2 diet were able to lower their LDL-cholesterol by 16% in three years. Heller et al (1992) studied a group of patients that had an acute myocardial infraction (AMI), to assess the efficacy of dietary intervention on the lipid profile and the quality of life six months after discharge from the hospital. No significant difference was seen in the lipid profile but the quality of life appeared to have improved as reported by the patients.

Denke et all (1994) after studying the individual responses to a cholesterol lowering diet in 50 men with moderate hypercholesterolemia, concluded that the Step 1 Diet is effective in lowering LDL-cholesterol level for many hypercholesterolemic men, and with appropriate counseling, outpatients can achieve results predicted by inpatient metabolic diet studies. The responsiveness for individuals is highly variable. The variability is influenced by both compliance and biologic factors. Denke et al (1994)

showed that 25% of the participants were biologically resistant to dietary changes. This has been identified in many other studies (Beyen & Katan, 1985; Katan et al, 1988; Jacobs et al, 1983; Cole et al, 1992). Also 25% of the dietary intervention participants were poor adheres to the program protocol (Denke et al, 1994). A similar percentage of nonresponders and noncompliers were reported in the Diet-Heart Feasibility Trial (NDHS, 1968).

Cost effectiveness of dietary treatment. Recent studies have found that health promotion programs lead to lower health care costs, reduction in absenteeism and to improvement in employees health and productivity (Bly et al, 1986; Gebhaedt & Crump, 1990). Bertera (1990) has estimated returns in savings of up to 1.45 dollars for each dollar invested in preventive programs. A review of the available studies of comprehensive worksite health promotion programs, by Pelletie (1991) showed that there is growing evidence that these programs are cost effective. Oldenburg et al (1995) examined the cost effectiveness of cardiovascular disease risk reduction programs. They found that behavioral counseling and risk factor education were both clinically and cost effective.

Adherence to lifestyle changes for a long period of time has not been successful (Carmody et al, 1980; Disman, 1988; Wadden and Bell, 1990; Rosi et al, 1990; National Statistics, 1989). The reason could be that the programs are not tailored to the needs of the individuals at a given time. Lifestyle change programs are not based on any systematic behavioral model. The transtheoretical model may be a useful tool in developing programs that will motivate individuals with elevated serum cholesterol to move to action and maintenance stage.

Transtheoretical Model

Discussing the difficulties of modifying a problem behavior, Mark Twain made this astute comment: "Habit is a habit, and not to be flung out of the window but coaxed downstairs a step at a time." (as cited by Prochaska and DiClemente page 3, 1992). Habit is defined by the Random House Dictionary of the English Language (1983), as "an acquired behavior pattern regularly followed until it has become almost involuntary". Behaviors involve repetitive and habitual action which are quite resistant to modification. Cessation of problem behaviors or installation of new behaviors does not occur automatically with one bold action or effort (Prochaska et al, 1992). Prochaska et al studied the decision making model of Janis and Mann (Mann, 1972) to develop the transtheoretical model.

Decision making is conceptualized by Janis and Mann in a conflict model. A conflict approach assumes that sound decision making involves careful scanning of all relevant considerations that enter into a decisional balance sheet of comparative potential gains and losses (Mann, 1972). The anticipated gains (or benefits) and the anticipated losses (or cost) can be categorized into four major types of consequences. These consequences of decision making are: gains or losses for self, gains or losses for significant others, self approval or disapproval, and approval or disapproval of others (Janis and Mann, 1977).

Horn (1976) outlines stages in the process of quitting smoking and talks about precontamplation of change, decision to change , short term change and long term change. Prochaska (1979) combined Janis and Mann's decision making model and

Horn's Personal choice health behaviors in several studies and developed the Transtheoretical Model.

The Transtheoretical model postulates that both the cessation of high risk behaviors and the acquisition of healthier alternatives involves progression through five stages of change: precontemplation, contemplation, preparation, action, and maintenance (DiClemente et al, 1991; Prochaska & DiClemente, 1983, 1984, 1992). The stages of change represent specific constellations of attitudes, intentions and behaviors that are relevant to an individual's status in the process of change. The stages are problem or behavior specific. Each stage of change represents a period of time as well as a set of tasks needed for movement to the next stage. Although the time an individual spends in each stage varies, the tasks to be accomplished are assumed to be invariant (Prochaska & DiClemente, 1986b).

Description of the Stages of Change

Precontemplation stage. Individuals in the precontemplation stage are unaware, unwilling or discouraged when it come to changing a particular behavior. Precontemplators are not convinced that the negative aspects of a behavior outweigh the positive. They are not considering changing the behavior in the foreseeable future and would be the least responsive to an intervention program focused on changing that particular behavior. In order to move to the next stage, individuals in this stage need to acknowledge or take ownership of the problem, increase awareness of the negative aspects of the problem and accurately evaluate self regulation capacities (DiClemente & Prochaska, 1985: Prochaska et al 1985).

Contemplation stage. Individuals in the contemplation stage are actively considering the prospects of change. These individuals engage in information seeking and begin to evaluate themselves in light of a particular target behavior. They tend to evaluate the losses and rewards that successful change will bring (Velicer et al, 1985). They evaluate the options but they are not prepared to take action at the present. Particular processes, such a consciousness raising and self reevaluation, are most important for individuals in the precontemplation stage (Prochaska et al, 1992).

Preparation stage. Individuals in the preparation stage are intending to take an action in the near future. They are on the verge of taking action and need to set goals and priorities accordingly. Often they are already engaged in processes which will increase self regulation and initiate behavior change (DiClemente et al, in press).

Action stage. This stage involves overt modification of the problem behavior. Individuals in this stage must have the skills to use key processes, such as counterconditioning, stimulus control, and contingency management to interrupt habitual patterns or behaviors and to adopt more productive patterns (Fitzgerald & Prochaska, 1988; Prochaska et al, 1992). Action individuals need effective strategies to prevent lapses from becoming complete returns to the problem behavior (relapse) in order to progress to the maintenance stage (Prochaska & DiClemente, 1986a).

Maintenance stage. Sustaining a behavior change is very important and difficult. Even after 6 months of action the problematic behavior is not completely extinguished and the new adaptive behavior not firmly established. This is particularly true if the environment is filled with cues that can trigger the problem behavior or the new behavior

occurs infrequently. In both cases maintenance can be problematic. Relapse is the norm in most behavior change attempts (Marlatt & Gordon, 1985). Counterconditioning and stimulus control are emphasized in this stage (Prochaska et al, 1990).

Measuring the Stages of Change

Several different measures have been used successfully to isolate the stages of change. Critical elements for accurate assessment of stage status would be attitudes, intentions and behaviors specific to each stage and each specific behavior.

Categorical classification. People who report the undesirable behavior and have no intention of changing the behavior in the next six months are classified in the precontemplation stage and if they intend to change within the next six months are classified in the contemplation stage. Subjects that indicate that they are planning to change behavior in the next six months or have already begun the changes (e.g. attend AA meetings) are classified in the preparation and action stage, and subjects that have changed the behavior in the last six months are classified as in the maintenance stage.

Classification by Pros and Cons. Prochaska et al (1994) examined the relationship among the stages of change and the pros (anticipated gains) and cons (anticipated losses) of 12 behaviors, including smoking, weight control, high fat diet, and exercise. For all behaviors people in the contemplation stage evaluated the pros of making a healthy behavior change as higher than the individuals in the precontemplation stage of change. No differences were reported on the cons of making the behavior change between the precontemplation and contemplation stage. For all behaviors the cons were lower for

subjects in action than in contemplation, however no differences in the pros were seen between the contemplation and action stage of change. Prochaska (1994) hypothesized that progress from contemplation to action would involve a relatively greater increase in the pros of a healthy behavior change than a decrease in the cons. This hypothesis was tested and confirmed by two different trials by Prochaska et al (Prochaska et al, 1992).

Contemplation Ladder. Rustin and Tate (1993) developed an alternative method of measuring the progress of smokers both towards abstinence and towards relapse. It includes attitudinal, historical and behavioral measures, and can be administered sequentially during a patient's treatment and it requires only a few minutes to administer. They named the model the "stages of change ladders". The stages of change ladders are an expanded measure of an analog ladder and DiClemente's stages of stage, in an attempt to measure subtle degrees of change in a smoker's thinking and behavior.

The "Contemplation Ladder" is another measurement of stage change among smokers (Biener, 1989). This is a visual analog scale on which smokers identify their stage of change with precontemplation on the bottom and maintenance at the top with a text description of each level. Subjects are asked to read the descriptions on the rungs of the ladders and indicate which rung they are on. The ladder has advantages over a standard, zero to ten horizontal scale, in having more visual impact, permitting a 10-15 word description of each level, and implying an upwards progression towards health.

Scale Scores and Profile Analysis. A questionnaire to measure the stages of change called University of Rhode Island Change Assessment Scale (URICA) has been developed (McConnaughy, Veliser & Prochaska, 1983). The questionnaire contains 32

questions relevant to the four stages of change. (The preparation stage is not included). The scale has four 8 item subscales. Each item is responded to on a five point Likert scale of agreement. Single subscale scores can be used independently for each stage or as predictor or criterion variables. Using the single subscale scores independently, however, appears to lose some important information about the relationship among the subscale scores (Prochaska & DiClemente, 1992). In most of the research using the URICA scale, a cluster analysis is done to isolate groups of individuals with specific patterns of subscale scores (McConaughy et al, 1983; McConnaughy et al, 1989; DiClemente & Hughes, 1990). The stability of the cluster analysis is quite remarkable (Prochaska & DiClemente, 1992). The scale has also been used for many behaviors such as alcoholism, smoking, exercise and low fat diets.

McConnaughy et al (1983) used the stages of change questionnaire and a clusters analysis on 155 adults involves in psychotherapy. The cluster analysis resulted in a total of 18 distinct clusters. Seven were classified as major clusters each involving 13-27 subjects. Two were classified as minor clusters each involving 5-6 subjects. The remaining nine clusters consisted of only 1-3 subjects and were considered uninterpretable. The major clusters are:

Cluster 1 was called the "Decision-Making" profile. There were 20 subjects in this group. They were characterized of below average scores in precontemplation and maintenance, and above average scores on contemplation and action. They were still contemplating their problem and yet they had begun to take some action.

Cluster 2 was called the "Maintenance" profile. There were 27 subjects in this

group. They were average on three of the scales (precontemplation, contemplation and action), and above average on the maintenance. Subjects in this profile were maintaining previous improvements, and tended not to rethink or take new action in the problem area.

Cluster 3 was called the "Participation" profile. There were 13 subjects in this group. They were below average on the precontemplation scale and above average on the contemplation, action and maintenance. These subjects were engaged in thinking about the problem, taking some action on changing it, and maintaining changes that were already made.

Cluster 4 was called the "Pre-Participation" profile. There were 27 subjects in this group. These subjects were slightly above average on contemplation, action, and maintenance. They do not ignore the existence of the problem. They were somewhat involved in thinking about acting on, and maintaining changes.

Cluster 5 was labeled as "Non-Contemplative action" profile. There were 14 subjects in this group. They were about average on precontemplation and action and below average on contemplation and maintenance. These subjects were not thinking about changing, nor were they maintaining any changes they may have made previously.

Cluster 6 was labeled as "Immotive" profile. There were 13 subjects in this group. They are about average on precontemplation and maintenance and below average on contemplation and action. These individuals were not contemplating change neither were they engaged in changing, rather they were maintaining the status quo.

Cluster 7 was called "Uninvolved" profile. There were 13 subjects in this group. They had average scores on precontemplation and contemplation, and below average

scores on action and maintenance. They were thinking about the problem but they were not involved in changing it.

Conclusion

To apply the transtheoretical model to a population which has a known increase in risk factors would allow one to use the model to find out at what stage of change individuals in the population are functioning. The appropriate intervention method could be then developed and applied.

Having an understanding of the stages of change process is very important. However further understanding of what it takes to move a person from one stage to the next is needed. Once that is understood a variety of programs can be developed for successful behavior change. If methods are developed to help individuals move to the action stage of change then all the modifiable risk factors are more likely to be changed.

A literature review of the traditional programs for exercise acquisition, smoking cessation, weight loss, heroin and alcohol addiction shows that these programs have not been effective. Approximately 50% of the participants in these programs drop out during the first 3-6 months (Carmody et al, 1980; Dishman, 1988) . This is in addition to those that relapse during the program itself. For smoking cessation 37% of the individuals that have been abstinent for 12 months will return to regular smoking (USDHHS, 1990). The success of weight loss programs appears to be only effective for one year or less (Wadden et al, 1989; Goodrick, 1991). The question still remains as to how the precontemplators and contemplators can be motivated to move to the next stage and eventually to the action stage. Helping relationships, consciousness raising, self liberation, self revaluation and

environmental reevaluation have been identified as processes by which people can induce a movement towards change from one stage to the next. The next question will be what causes the raising of consciousness or self liberation, self reevaluation etc. (Watson & Tharp, 1989). Will the knowledge of a risk factor for a disease such as hypercholesterolemia or the diagnosis of a disease such as ASHD cause an individual to engage in helping relationships, consciousness raising, self liberation and self reevaluation? This needs to be studied.

Summary

Several lifestyle related risk factors contribute to the dysfunction of the vascular endothelium. These risk factors are: hypertension, tobacco smoking, diabetes, and hypercholesterolemia. Studies have shown that lowering serum total cholesterol and LDL-cholesterol improves the function of endothelium in the coronary arteries for individuals that have atherosclerotic heart disease. There is evidence that endothelial dysfunction is present in the brachial artery. The effects of lowering serum cholesterol level on the brachial arteries of otherwise normal individuals has not been determined. The present study will look at the effects of lowering cholesterol on the vasodilation of the brachial artery. Only individuals that have hypercholesterolemia (serum cholesterol level above 240 mg/dl and LDL-cholesterol above 160 mg/dl) but have no diabetes, hypertension or are smoking will be allowed to enter the study.

Hypercholesterolemia is very prevalent in the United states as well as other industrialized countries. Cholesterol lowering medications are available however the first choice of treatment is lifestyle change, which include nutrition, exercise and stress

management (Watts et al, 1992).

The lifestyle programs can be inpatient or outpatient based. The inpatient studies show a great success in lowering the serum total cholesterol and LDL-cholesterol level by lifestyle in a short time (McDougall et al, 1995). There are few studies that support the success of lifestyle change on outpatient basis (Watts et al, 1992; Denke & Grundy, 1994; Hunninghake et al, 1993). These studies report that individuals who adhere to the study dietary protocol are successful in reducing their total cholesterol and LDL-cholesterol. Both inpatient and outpatient programs report a significant decrease in HDL-cholesterol. Denke et al, 1994 showed that 50% of men with LDL-cholesterol greater than 190 mg/dl who are candidates for cholesterol lowering drugs can avoid taking the cholesterol lowering drug by employing the Step 1 Diet. Seventeen percent of the patients that have LDL-cholesterol level greater than 160 mg/dl , and have two or more risk factors for CAD can avoid taking the cholesterol lowering drug with Step 2 diet.

No changes in the mood status of the participants in lifestyle changes, mainly exercise have been reported in the literature (Blumenthal et al, 1988; Erdman et al, 1986; Dracup et al, 1991).

Not much information was found on long term adherence to lifestyle changes, however the National Statistics indicate that only a small percentage of the U.S. population (7%) has actually achieved a fat consumption level less than 30% of the daily caloric intake (LSRO, 1989).

A great need exists for the development of efficient and effective outpatient programs for long term lifestyle modification in order to reduce serum cholesterol in

hypercholesterolemic individuals and to prevent others from acquiring high serum cholesterol levels. The Transtheoretical model may be a tool to consider in developing such programs. Successful lifestyle modification that could bring a reduction of cholesterol levels may bring about many health benefits such as reversal of endothelial dysfunction, and decrease in the incidence of atherosclerotic heart disease.

The present study will attempt to lower cholesterol in one group with medication and another group with lifestyle changes in an outpatient setting, the results will be compared to a placebo control group. Also the Prochaska and DiClemente's stages of change and the mood status of the individuals will be assessed on all participants.

CHAPTER 3

METHODOLOGY

This research is a true experimental study, involving direct manipulation of cholesterol levels, a control group, randomization and comparison. The graphical representation is:

O1	X1	O2	(lifestyle intervention)
O1	X2	O2	(medication)
O1		O2	(placebo group)

Recruitment

Subjects. The number of subjects in each group were 17 or greater. This is based on the assumption of what Cohen (1977) calls a large effect size at an α of 0.05 and a power of 70%. The assumption of a large effect size seems tenable because a similar study by Creager et al (1990) had an effect size that would have generated power of 80% with only 8 subjects per group. The criteria for selecting subjects were as follows: Individuals with serum total cholesterol levels above 240 mg/dl and/or serum LDL-cholesterol levels greater than 160 mg/dl. Individuals who were smoking, who had hypertension, diabetes or ASHD were excluded.

Recruitment methods. The subjects were recruited in several ways:

1. Posters inviting individuals to participate were placed at the Jerry L. Pettis Veteran Affairs Medical Center and Loma Linda University Medical Center at several key locations.

2. Brochures regarding the research project were given to the Preventive Care Specialist at the Center of Health Promotion Health Screening Fairs to give to any individual that was identified as having serum cholesterol greater than 240mg/dl.

3. During the National Laboratory Week, Loma Linda University Medical Center Laboratory held a cholesterol screening. A pamphlet informing people about the study was mailed with the report of each high cholesterol level.

4. Pamphlets were mailed by the San Bernardino Blood Bank to individuals that donated blood and were identified as having high cholesterol.

Methods 1, 2, 3, and 4 described above recruited 127 individuals who contacted the Cardiology Department at the Jerry L. Pettis Veterans Affairs Medical Center. Only 46 were qualified to participate and were actually tested. Six of those chose not to participate in the study after they were tested. Their reasons being vacation plans or other obligations that interfered with the research protocol. This small sample size lead to the use of three other recruitment methods.

5. Patients were identified from Jerry L. PETTIS Veterans Affairs Medical Center pharmacy and laboratory data base who had serum cholesterol greater than 240 mg/dl and had no diabetes, hypertension or ASHD. Their health status was determined by the lab results and by the records of medication prescriptions (absence of insulin, nitrates and hypertensive medications prescription). A letter was mailed to 237 individuals inviting them to participate in a lecture on cholesterol. The lecture focused on the significance of elevated cholesterol and its proper management. Lectures were offered four different times to accommodate as many patients as possible. A set of slides from the American

Heart Association/ Bristol-Myers Squibb was used for these presentations, making all four lectures consistent with each other. Sixty three individuals attended these lectures. At the completion of each lecture a description of my research was briefly presented. The participants were offered the opportunity to join the research study. Thirty-six individuals agreed to enter the study. After interviewing and evaluating their cholesterol level only 10 of these individuals met all the criteria and qualified to participate.

6. One hundred seventy-four patients from Jerry Pettis Memorial Hospital were contacted by telephone and asked if they were interested in participating in the study. Only 12 patients that met the criteria showed an interest in participating in the study. Some were disqualified because they were smoking or were on cholesterol lowering medication. Out of those twelve individuals none of them actually participated in the study.

7. A list of 129 patients with serum cholesterol levels greater than 240mg/dl was obtained from the Loma Linda University Center of Health Promotion. These patients were contacted by telephone and asked if they were interested in the study. Ten of those indicated they were interested but only three actually participated in the study.

In summary, a total of 667 individuals were contacted. Out of these individuals 27.7% (185) qualified to participate but only 28.6% (53) of those qualified actually entered the study.

Study Design

Experimental conditions and sample size. Study subjects were randomly assigned to three different groups. Randomization was stratified by age to ensure equatable age distribution. The three groups were: a lifestyle change group, a medication

group and a placebo group. Seventeen individuals completed the lifestyle group program. Seventeen individuals completed the program in the medication group. Nineteen individuals completed the placebo group. The duration of the research intervention was a total of eight weeks. One week for pretesting, six weeks for intervention and one week for posttesting. Because not all participants were recruited at the same time, the interventions were held tree different times. There were 4 to 8 individuals in each group during each session.

Lifestyle group intervention. The lifestyle change group participated in a group program at the Loma Linda University Center of Health Promotion and at the Loma Linda University School of Public Health. The meetings were held twice a week for three hours each. The group program included lectures on nutrition, exercise and stress management. A low fat and high fiber diet was taught. The recommended diet consisted of 15% fat, 10-15% protein, 70-75% carbohydrate and at least 25 gm fiber per day. The participants were advised to reduce meat intake to once or twice a week and to chose the leaner varieties. They were advised to use nonfat or 1% fat milk. They were also strongly advised to substitute their fat intake with olive oil or canola oil. Fresh fruits and vegetables were recommended (see appendices B1-12 for more information on the lectures). Exercise such as brisk walking or jogging, and bicycling for 30 min at least four time a week was strongly advised. Participants attended stress management classes during each intervention session. A complete meal was provided for them at each meeting. This was designed to teach the participants to prepare low fat meals. The spouses were invited to attend all sessions as well. The individuals had control over their

lifestyle. With the exception of the two meals per week offered during group meetings, the individuals had to prepare their own food.

Medication group intervention. The medication group was given 20 mg of Pravastatin an HMG CoA reductase inhibitor cholesterol lowering medication which was provided by the pharmaceutical company, Bristol-Myers Squibb.

Instructions were given to take one tablet with water each night before going to bed. If for any reason the medication was not taken they were instructed to leave the pill in the bottle and return the bottle to the researcher at the end of the six weeks. A physician's telephone number was written on the bottle so that they could call at any time if they experienced any side effects.

Control group. The control group was given placebo capsules for six weeks. They were given the same instructions as the medication group. The same physician's telephone number was also written on the bottles. Individuals were not informed as to whether they were taking the medication or the placebo.

Measurements

Brachial artery. EDRF itself was not measured due its very short half life and the difficulty in measuring it accurately. Measurements of brachial diameter of the right arm at longitudinal and transverse plane were taken before and 45 seconds after mechanical induction of hyperemia. The brachial artery diameter was measured about one inch above the antecubital fossa where the artery becomes linear (not curved). Hyperemia was induced by inflation of a pneumatic tourniquet to a pressure of 220mm Hg for 5 minutes then released. The targeted artery diameter, was measured using the

Acuson 128xP/10 system with 7.0-MHZ linear array transducer which is a high-resolution ultrasound image scanner located at the cardiology section at the Loma Linda University Medical Center. The technique for measuring these parameters has been described by Celermajer at al (1992) using the same instrument.

All measurements on the brachial artery were read at the Cardiology Department at Loma Linda University Medical Center. Super VHS video tape recordings of each sonogram reading were obtained and results were later read off line by two independent cardiologists. Each reading was labeled by a randomly assigned number so that the reader was unable to identify the patient or the group they were in or whether the reading was pre intervention or post intervention.

Instrument validity. Small changes in vessel diameter can be reliably detected by means of high-frequency linear array transducer. The theoretical limit of axial resolution of 7.0 MHZ ultrasound in the near field is about 0.1-0.2 mm depending on the number of cycles within each ultrasound pulse (Wendelhag et al, 1991). Ultrasonic calipers are accurate to 0.1 mm. Beam plot and phantom experiments have shown that changes in axial distance from the transducer of 0.1 mm or more can be visualized and measured accurately. To assess the accuracy of detecting small changes in the vessel diameter using a 7.0-MHZ linear array transducer and a standard Acuson 128XP/10 system several studies have been done. Celermajer et al (1993) constructed a phantom that contained 10 "arteries" located 10 mm below the phantom surface. These arteries mimic the range of diameters of normal male and female brachial arteries and were arrange in random order. Two operators scanned each artery three times with the same instrument settings used in

clinical studies, with images recorded on super -VHS videotape for later off line analysis. Four independent observers, who were unaware of the characteristics of the phantom analyzed the scans on three different occasions in random order. The mean error of all measurements was <0.05 mm and no estimate of diameter difference was >0.1 mm error.

Celermajor et al (1992) checked the reproducibility and repeatability of the instrument by using 127 subject visits, two observers for each visit and a third observer for 30 cases. The mean range for interobserver difference for the measurement of percent flow-mediated dilation was 1.7 % (0-7). From the full nested analysis of variance, the estimated coefficient of variation was 1.4%.

The study of repeatability was based on 21 subjects (12 controls, 6 smokers, 3 with coronary disease) who underwent repeat scans. In each case there was a directionally similar response to increased flow and to glyceryl trinitrate. Normal subjects showed dilation in response to an increase in flow in each occasion although the extent of increase varied and the abnormal subjects had reproducible failure to dilate. The mean range of across visits of observed percent flow-mediated dilation was 2.8% (0-10%). From the nested analysis of variance the estimated coefficient of variation between visits was 2.3%. *Blood Pressure.* Blood pressure was taken on the left arm after the brachial artery diameter was measured. A manual pneumatic tourniquet was used to obtain the blood pressure. It was measured only once by the same echosonographer that took the arterial diameter measurements. Blood pressure was taken pre and post intervention.

Blood Tests. Participants were tested with a 12 hour fasting lipid profile , as well

as an AST and ALT analysis (liver enzymes). The lipid profile included: total cholesterol, LDL-cholesterol, HDL-cholesterol and Triglycerides. The blood tests were done both before and after the intervention. All blood analysis were done at the Jerry L. PETTIS Veterans Affairs Medical Center hospital laboratory.

Weight: The weight was self reported by the subjects before and after the intervention using their home scales.

Nutritional status. The Nutritional Profile Plus questionnaire was used to assess the nutritional status of each individual pre and post intervention.

Stages of change:. Subjects were given the University of Rhode Island Assessment Scale (URICA) which consists of a set of 32 questions designed to measure the four stages of change: precontemplation, contemplation, action and maintenance (DiClemente et al, 1991; Prochaska & Diclemente, 1983, 1984, 1992). The transtheoretical model postulates that both the cessation of a high risk behavior and the acquisition of a healthier alternative involve progression through the four stages of change as stated above. The individuals who are in the action stage are those who are ready and willing to change a behavior (DiClemente et al, 1991; Proshaska & DiClemente, 1983, 1984, 1992).

Mood state test: The Profile of Mood States (POMS) was used to assess the mood status of the subjects before and after the intervention. The POMS measures six identifiable mood or affective states: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment. (McNair et al, 1992).

CHAPTER 4

RESULTS

Data was entered in the SPSS for windows program (version 6.1) and analyzed. The pre-intervention data from all three groups was compared to the post-intervention data. A repeated measures analysis of variance (ANOVA) was performed. The results were used to compare groups.

Demographics

There was no significant difference in the age, gender and weight distribution among the groups at the pretest (see table 1).

Participation

Groups. There were 17 subjects in the lifestyle group, 17 subjects in the medication group and 19 subjects in the placebo group that completed the program. Only 16 subjects from the placebo group were used for data analysis. Three of the individuals from the placebo group were excluded from the calculation. One individual had taken Pravastatin for a month subsequent to his lipid profile. He also at that time became a strict vegetarian with the rare addition of fish to his diet. Another person was excluded because her spouse had a heart attack about the time that she entered the study and his physician advised them to change their eating habits. The spouse was on Pravastatin and this individual knew from the look of the capsule that she was on placebo. She changed her life style and also she got heavily involved in water aerobics. In fact she was teaching

Table 1. Pretest Age, Gender and Weight Means and 95% Confidence Intervals

GROUP	*n*	AGE (years)	GENDER	WEIGHT (lbs)
Lifestyle	17	51.8 ±3.4	65% males	187 ± 23.7
Medication	17	51.6 ± 2.8	53 % males	180 ± 26.2
Placebo	16	55.7 ± 2.8	61 % males	177 ± 15.8
*p**		0.384	0.773	0.78

* Significance test from ANOVA

water aerobics by the end of the study. A third individual completed all phases but did not have his post intervention blood lipid profile done.

Lifestyle group. Twelve lectures were offered for each of the three lifestyle groups for a total of 36 lectures all together. There were 17 subjects and each was offered 12 lectures. If class attendance was 100% there would have been 204 occasions (12x17) during which individuals might participate. However there were 19 absences. Thus the compliance of the individuals in the life-style group for class attendance was 90.7% (attendance on 185 occasions out of 204). Compliance with the diet and exercise were self reported. The data were obtained from the Nutritional Profile Plus questionnaire that was completed by the individuals.

Medication group. All participants in the medication group were advised to take the prescribed medication according to the physician's instructions. Since the participants were instructed to return the medication containers with all remaining pills we were able to calculate the percentage of pills taken by each participant. Compliance was calculated to be 91.5%.

Control group. All participants in the control group were given a placebo capsule and the same instructions as the medication group. The percentage of placebo capsules taken by the participant was 91.1%. One patient was excluded because he failed to take the capsules for a 30 day period which make the compliance rate for him 38%. This person was also not included in the data analysis because he failed to have his serum lipid profile done at post intervention.

Serum Lipid Values

The mean serum lipid values for each group were calculated for pretest and posttest values. The means and significance tests for the differences are found in table 2. The total cholesterol and LDL-cholesterol level, as well as the LDL/HDL ratio dropped significantly between the pretest and the posttest. There was a significant interaction. The total cholesterol, LDL-cholesterol, and the LDL/HDL ratio improved in the life style and medication group but not in the placebo group. No differences were observed for HDL-cholesterol and triglyceride levels between the pretest and posttest or between the groups. The lifestyle group lowered their total cholesterol by 9.4%, the LDL-cholesterol by 15.1% and LDL/HDL ratio by 13.5% and increased their triglyceride levels by 13.4% during the six week intervention period. The medication group lowered their total cholesterol by 16%, their LDL-cholesterol by 19.9%, their LDL/HDL ratio by 22.7% and the triglyceride level by 12.2% in the six week intervention period

Lifestyle Changes

The means for lifestyle changes for each group were calculated for pretest and posttest values. The means and significance tests for the differences are found in table 3. There was a significant interaction between time and treatment for nutritional score, percent fat intake, percent saturated fat, fiber intake, and time of moderate exercise. There was an increase in nutritional score and fiber intake in the lifestyle group, however no changes occured in those values among the medication and

Table 2. Pretest and Posttest Means and 95% Confidence Intervals for Blood Lipid Values.

Group	Total Chol. (mg/dl)		LDL (mg/dl)		HDL (Mg/dl)		Triglycerides (mg/dl)		LDL/HDL	
	M	*n*	*M*	*n*	*M*	*n*	*M*	*n*	*M*	n
Pre-intervention										
Lifestyle	267±13.6	17	192±12.6	14	39±6.7	14	196±63	16	5.2±0.8	14
Medication	276±16.0	17	191±19.8	13	48±9.9	13	254±119	17	4.4±0.9	13
Placebo	283±14.0	16	199±12.0	14	45±5.1	15	198±55	16	4.7±0.7	14
Post-intervention										
Lifestyle	242±16.7	17	163±18.2	14	37±4.8	14	223±56	16	4.5±0.5	14
Medication	231±18.3	17	153±13.9	13	49±8.5	13	223±115	17	3.4±0.6	13
Placebo	282±16.2	16	195±12.6	14	44±5.4	15	226±55	16	4.6±0.7	14
Significance tests										
Group	0.004		0.013		0.075		0.836		0.077	
Time	0.000		0.000		0.530		0.513		0.000	
Interaction	0.001		0.007		0.437		0.059		0.016	

Table 3. Pretest and Posttest Means and 95% Confidence Intervals for Lifestyle Changes.

Group	*n*	Weight (lbs)	Nutritional Score	Fat% (per day)	Saturated Fat %/day	Diet. Chol mg/day	Fiber (gm/day)	Moderate Exercise (hrs/day)	Heavy Exercise (hrs/day)
Pretest									
Lifestyle	17	187±23.7	59.6±7.0	31.8±2.9	10.6±1.5	320±109	21.9±6.4	1.0±0.7	0.55±0.74
Medication	17	181±26.2	55.2±8.9	34.7±5.9	11.8±3.2	326±117	22.4±7.4	1.0±0.6	0.50±0.46
Placebo	16	177±15.8	59.5±10.2	30.1+4.3	10.1±2.0	449±250	23.5±5.9	2.3±1.1	0.66±0.57
Posttest									
Lifestyle	17	182±21.6	81.6±4.6	19.6±2.3	5.5±1.1	159±60	29.2±5.6	1.4±0.7	0.44+0.52
Medication	17	179±25.3	58.8±9.2	30.3±5.6	10.3±2.6	316±112	23.4±8.1	2.1±0.8	0.59±0.44
Placebo	16	176±16.7	59.0±10.2	29.0±5.2	10.3±2.2	297±91	19.1±5.5	1.7±1.0	0.97±1.02
Significance test									
Group		0.873	0.024	0.053	0.084	0.230	0.545	0.243	0.678
Time		0.002	0.000	0.000	0.000	0.006	0.424	0.196	0.557
Interaction		0.059	0.000	0.000	0.000	0.188	0.018	0.008	0.596

placebo groups. The percent fat and saturated fat intake decreased in the lifestyle group but no changes were observed in the medication and placebo groups. A drop in weight was observed in the lifestyle group but it was not significantly larger than the change in the other groups. An increase in moderate exercise was observed in the lifestyle and medication group, whereas the placebo group experienced a drop in the time of moderate exercise per week. No significant effects were observed for the amount of time of heavy exercise per week, however a slight increase was observed in the placebo and medication groups and a slight decrease in the lifestyle group.

Blood Pressure and Brachial Artery Diameter

There was significant interactions involving the systolic and diastolic blood pressure. There was a drop in the systolic and diastolic blood pressure among the lifestyle and medication groups while the systolic and diastolic blood pressure increased in the placebo group. The means and significance tests for the systolic and diastolic blood pressure are found in table 4.

The brachial artery diameter was measured longitudinally and transversely. There were three reading for each brachial artery diameter measurement. The echosonographer's readings and the readings of two independent observes that read the video taped results as mentioned in the methods section. The correlation coefficient was greater than 0.85 for both the longitudinal and the transverse readings before and after intervention. The scattergram was in agreement with the correlation tests (see appendix B scatterplots of interrater aggreement). The means and the significance tests for the

Table 4. Pretest and Posttest Means and 95% Intervals for Arterial Measurements

Group	Systolic Blood Pressure		Diastolic Blood Pressure		Long. Arterial Diameter Ratio		Transv. Arterial Diameter Ratio	
	M	*n*	*M*	*n*	*M*	*n*	*M*	*n*
pretestPretest								
Lifestyle	122.6±6.0	16	82.4±3.7	16	1.093±0.049	17	1.089±0.056	17
Medication	130.2±6.9	17	82.6±2.9	17	1.086±0.030	17	1.060±0.030	17
Placebo	123.6±5.8	16	74.0±4.8	16	1.090±0.034	16	1.098±0.064	16
Posttest								
Lifestyle	116.4±6.3	16	76.0±4.6	16	1.113±0.058	17	1.086±0.036	17
Medication	124.1±5.2	17	82.0±3.7	17	1.116±0.038	17	1.104±0.042	17
Placebo	130.2±8.9	16	82.3±5.8	16	1.111±0.049	16	1.283±0.279	16
Significance test								
Group	0.071		0.201		0.993		0.143	
Time	0.338		0.711		0.130		0.072	
Interaction	0.017		0.000		0.958		0.164	

differences in diameter were calculated and are found in table 4. The ratio of the mean brachial artery diameter for pre-intervention and post-intervention values was used for the ANOVA. No significant difference was observed between the pre and post intervention values (see table 4). The scaterplot was examined to see if there was any nonlinear association but none was found.

The partial correlation coefficient between lipid profile difference and arterial diameter difference was done controlling for age and gender (see table 5). No correlation was seen except between the triglyceride difference and the transverse diameter difference. However if Bonferoni adjustments were made for the number of significance tests done this would not be significant.

Profile of Mood States

The data from the Profile of Mood States (POMS) was analyzed using the multiple analysis of variance (MANOVA). No significant differences were observed among the groups , however there was a significant drop in fatigue scores from pretest to posttest for all groups (although if a Bonferoni adjustment were made for the number of significance tests done this would not be significant) . Also a nonsignificant fall from pretest to posttest was seen in depression and tension in all groups. The means and significance tests for anger, confusion, depression, fatigue tension, and vigor are shown in table 6.

Table 5. Partial Correlation Coefficient Between Lipid Difference and Arterial Diameter Difference Controlling for Age and Gender

Lipids	Longitudinal Arterial Diameter Difference			Transverse Arterial Diameter Difference		
	Lifestyle	Medication	Placebo	Lifestyle	Medication	Placebo
Chol. diff	-0.23	-0.08	0.19	0.13	-0.44	0.06
n	17	17	16	17	17	16
p value	0.413	0.768	0.510	0.651	0.101	0.840
LDL diff	0.18	0.07	0.01	-0.32	0.23	-0.17
n	14	13	15	14	13	15
p value	0.569	0.842	0.985	0.304	0.488	0.573
HDL diff	0.18	-0.43	0.03	0.03	0.22	-0.11
n	14	13	15	14	13	15
p value	0.569	0.187	0.917	0.938	0.517	0.727
Trigl. diff	0.05	-0.21	-0.02	0.01	-0.55	-0.26
n	16	17	16	16	17	16
p value	0.857	0.459	0.934	0.984	0.034	0.372

Table 6. Pretest and Posttest Means and 95 % Confidence Intervals for the POMS

Group	Anger	Confusion	Depression	Fatigue	Tension	Vigor
Pretest						
Lifestyle	6.94±4.91	10.53±1.91	6.71±4.71	7.41±3.86	12.35±2.54	18.50±2.92
Medication	8.82±4.30	10.18±2.00	8.42±4.77	8.44±3.46	16.00±4.41	17.65±2.49
Placebo	7.88±2.95	10.81±1.75	7.66±3.37	7.62±3.46	14.27±4.16	19.04±2.21
Posttest						
Lifestyle	5.23±3.56	10.65±1.52	5.35±3.69	5.41±3.09	14.85±3.22	18.92±3.67
Medication	6.53±3.88	9.83±1.76	6.06±3.01	6.69±2.80	15.49±2.46	19.29±2.61
Placebo	7.10±3.44	10.50±1.82	7.12±4.27	6.94±3.27	16.77±3.18	19.37±3.34
Significance tests						
Group	0.751	0.806	0.817	0.841	0.512	0.912
Time	0.120	0.662	0.091	0.040	0.070	0.268
Interaction	0.828	0.874	0.745	0.720	0.222	0.701

Stages of Change

A seven cluster k-means cluster analysis was done on the University of Rhode Island Change Assessment Scales. Seven clusters were chosen since this was the number formed by McConnaughy et al (1983). However there was very little difference between some of the clusters and some had as few as 2 cases. Therefore a four cluster k-means cluster analysis was done based on the appearance of the dendrogram in a hierarchical cluster analysis. The number of cases in each group and the means for the pre-contemplation, contemplation, action and maintenance groups are found in table 7 for the four clusters. All groups were low on precontemplation, highest on contemplation and in between on precontemplation and contemplation for action and maintenance. Figure 1 graphically shows each of the four clusters. The graph for cluster 3 resembles the Decision making profile found by McConnaughy et al (1983) and the cluster 4 resembles the Participation profile also found by McConnauaghy et al (1983). Figure 2 show the pretest and posttest values of all the groups together. Again it resembled the Decision making profile. There were no interactions for the stages of change scales except for the action stage as seen on table 8. The action stage scores of the lifestyle group went up while the action stage for the medication and the placebo either dropped or remain the same. No correlation was seen between the difference in pretest and posttest lipid profile and the stages of change

Table 7. Means and 95% Confidence Intervals for the Four Cluster Analysis for URICA.

Cluster	cases	Precontemplation	Contemplation	Action	Maintenance
1	4	13.25±3.99	32.50±2.98	21.00±3.42	20.25±5.51
2	28	18.14±1.10	32.19±0.67	31.04±0.94	25.64±1.55
3	8	11.87±1.79	36.6±1.60	32.37±1.02	21.93±2.39
4	10	11.30±0.62	37.8±1.33	33.60±3.18	33.40±2.15

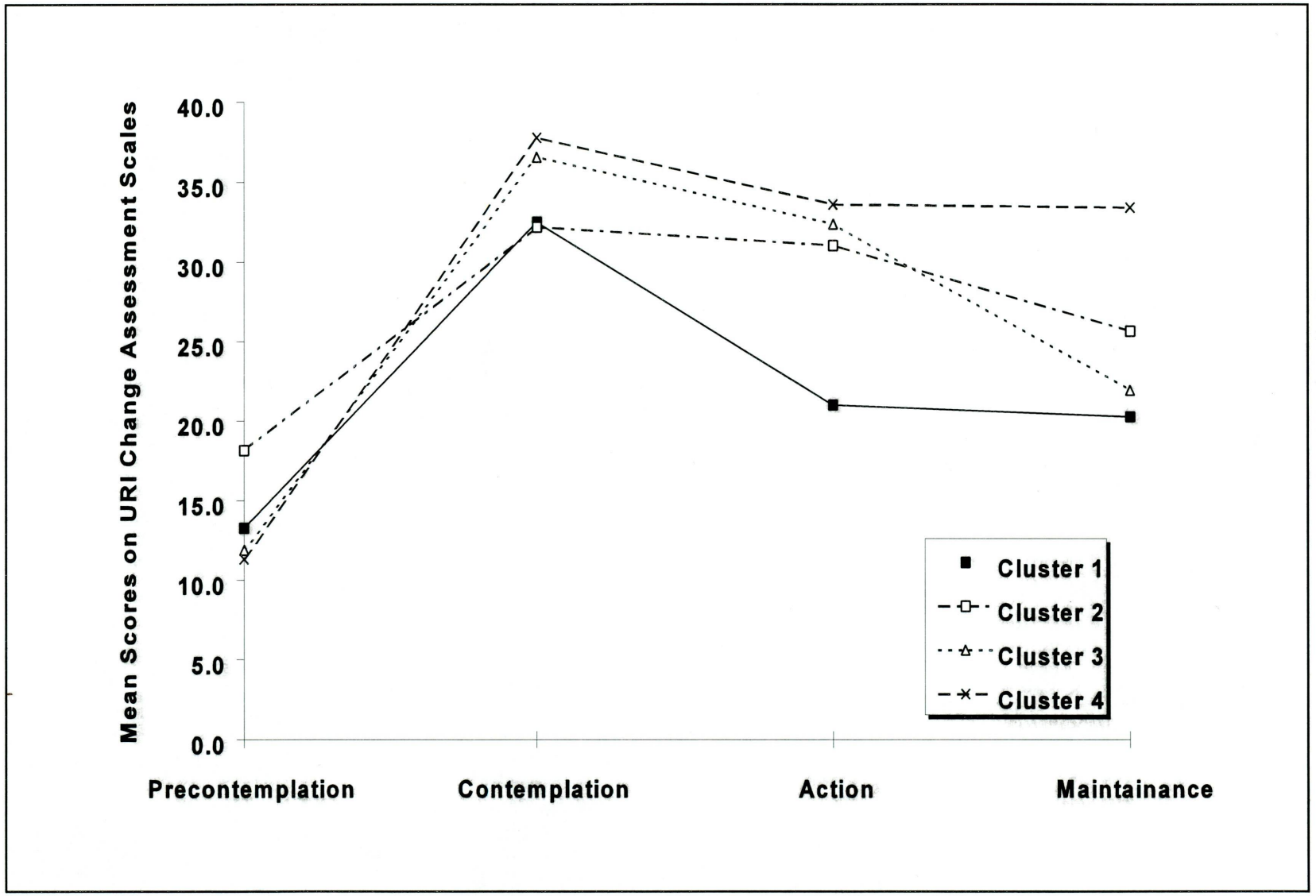

Figure 1. Mean scores for four groups created by cluster analysis for four stages of change scores.

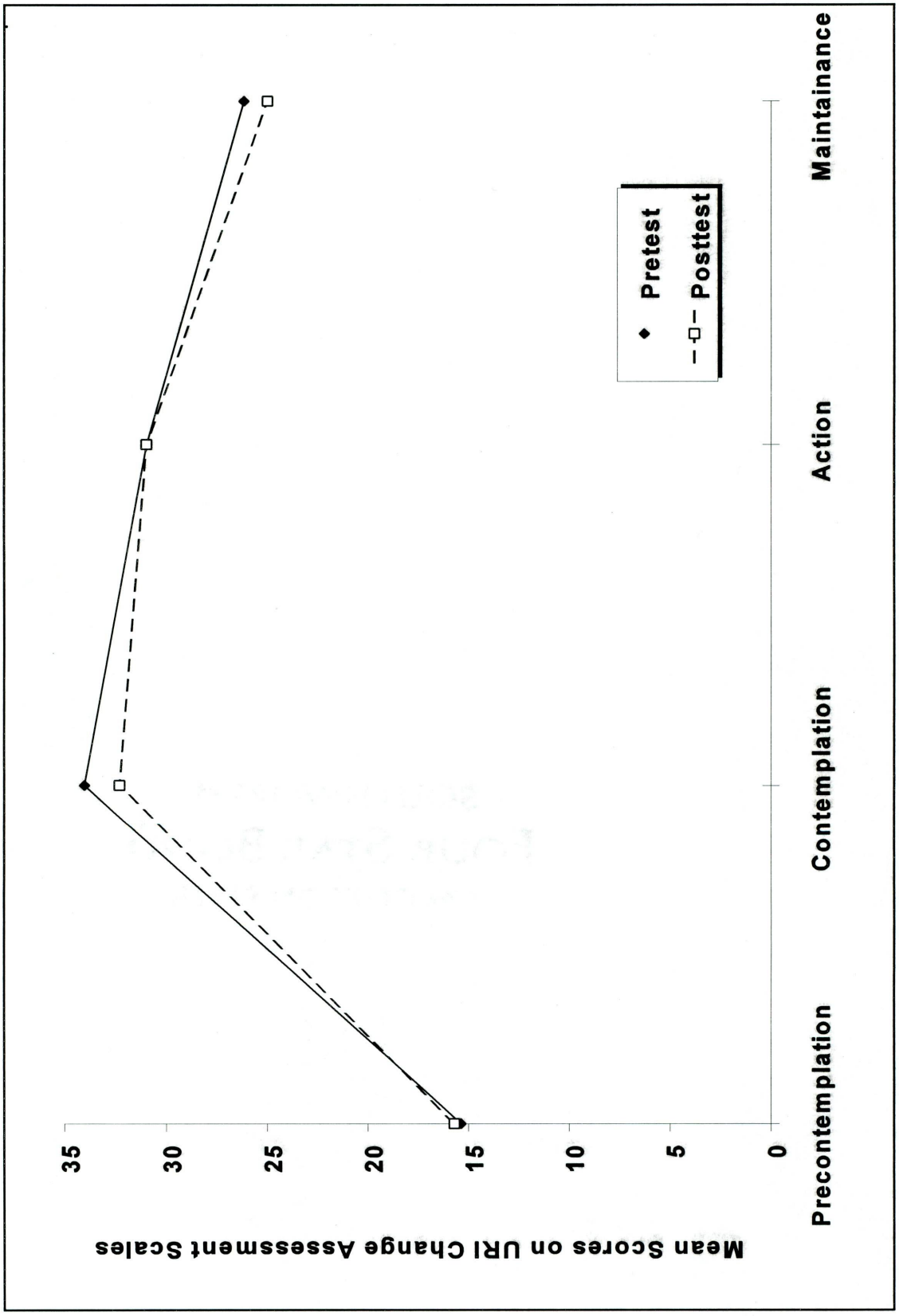

Figure 2. Mean scores before and after intervention on four stages of change.

Table 8. Pretest and Posttest Means and 95% Confidence Intervals for the URICA Scores

Group	Precontemplation	Contemplation	Action	Maintenance
Pretest				
Lifestyle	14.71±1.89	34.77±1.85	30.94±2.76	28.18±3.23
Medication	14.06±1.93	34.39±1.78	32.53±1.21	28.08±3.05
Placebo	17.50±2.37	32.84±1.12	29.31±2.49	26.12±2.27
Posttest				
Lifestyle	13.94±1.78	32.71±1.62	32.81±2.13	25.00±3.27
Medication	15.94±1.62	32.47±1.08	30.18±2.09	26.65±2.22
Placebo	17.31±1.88	31.69±1.08	29.87±2.21	23.25±2.87
Significance tests				
Group	0.020	0.138	0.206	0.139
Time	0.558	0.002	0.958	0.191
Interaction	0.104	0.739	0.006	0.218

CHAPTER 5

DISCUSSION

The purpose of this research was to look at the effects of lowering cholesterol by lifestyle and medication on the brachial artery vasodilation in six weeks and to find out whether there were any differences between the outcomes. To assess the effects of lowering cholesterol on the brachial artery vasodilation, the serum lipid profile and the brachial artery diameter pre and post occlusion by pneumatic tourniquet were measured pre and post- intervention. The mood status was assessed by using the POMS pre and post-intervention. The URICA was used to assess the stage of change of each individual and whether there was any difference in the outcome of the individuals who were in the action stage and the other individuals.

Serum Lipid Values

The total cholesterol, LDL cholesterol and the LDL/HDL ratio were reduced in the medication and lifestyle group. No changes were observed in the HDL-cholesterol among the three groups. There also was no change in the total cholesterol, LDL-cholesterol and LDL/HDL ratio values in the placebo group. There was no significant difference in the total cholesterol reduction between the lifestyle and the medication group. However, the lifestyle group could have possibly dropped their cholesterol level more had they been living under controlled conditions. The individuals who participated in the lifestyle group were living at home. They were purchasing and preparing their own food and were exercising on their own. The majority of them had families to take care of.

They made changes as they increased their knowledge on lifestyle and lowering cholesterol issues. However, the changes could have been accomplished immediately if they had been living in a controlled environment. The literature supports that strict adherence to a healthy lifestyle will produce the same or even better results than medication in many cases (Ornish et al, 1990; Ornish, 1990; McDougall et al, 1995; Denke & Grundy, 1994). Considering the difficulty of the change process that these individuals had to go through, they were very successful in reducing their blood lipid values. They were taught that their diet should consist of 70-75% carbohydrates, 12-15% protein and 15% fat. In addition, 30-40 min aerobic exercise at an appropriate intensity level for each individual's fitness level for 3-5 times per week was strongly encouraged. According to the self reported Nutritional Profile Plus report the lifestyle group decreased their fat intake by 38%, the medication group decreased fat intake by 4.4% and the placebo group by 3.7%. There is a possibility that the lifestyle group may have reported what they wanted the researcher to hear or what they knew they ought to do rather than what their actual diet was at that time, though the changes in blood lipids suggests that some dietary change must have occurred. The medication and placebo groups may have also tried to report what they thought the researcher wanted to hear, however they were not likely as familiar with the ideas of the researcher as the lifestyle group were. The medication group lowered their fat intake by 13% in combination with cholesterol lowering medication which would cause an additive effect on the serum cholesterol reduction. The HDL-cholesterol is expected to drop significantly (14-16%) with very low fat diets (Ornish et al, 1983; Bernard, 1989; McDougall et al, 1995), However in my

study there was no change in the HDL-cholesterol in the lifestyle group. This is a positive effect since HDL-cholesterol has an inverse relationship with CHD. This effect may be attributed to the fact that the individuals in the lifestyle group were advised to use olive oil or canola oil as their main source of fat intake (see appendices A, lifestyle lectures). There are no dietary records to show how much mono-unsaturated fats they were consuming, however the reported data shows that the mean fat percent intake in the lifestyle was was 19.6% and the mean saturated fat percent was 5.5%, therefore the majority of the fat intake was mono-unsaturated and polyunsaturated fat.

Blood Pressure and Brachial Artery Diameter

Blood pressure. Both the diastolic and the systolic blood pressure were reduced in the lifestyle group. The systolic blood pressure was reduced in the medication groups but no change in the diastolic blood pressure occurred. There was an increase in both the systolic and diastolic blood pressure in the placebo group. Possibly this was due to changes in exercise. Both the lifestyle and medication group reported an increase in moderate exercise, while the placebo group reported a decrease in moderate exercise. However using reports of moderate exercise as a covariate did not eliminate the effect. The lifestyle group were taught stress management during each intervention session. Stress has been identified as a risk factor for hypertension. It could be that the lifestyle group, using the stress management techniques they learned in class, were able to handle their stress better resulting in a decrease of their blood pressure. However that does not explain why the medication group lowered their systolic blood pressure. It could be possible that the vasodilation improved enough to influence the blood pressure, but not

enough to be detected with the acuson ultrasound instrument.

Arterial diameter. No difference was found between the arterial diameter before and after the intervention and no relationship was found between the cholesterol changes and the brachial artery diameter. There are several factors that may have influenced this outcome (see section on strengths and limitations). However, even if all the factors were corrected I still cannot be sure that the outcome would have been any different. The studies found in the literature (Leung et al, 1993; Egashira et al, 1994; Treasure et al, 1995) that evaluated the effect of lowering cholesterol on the EDRF and found significant improvement in the vasodilation of the coronary arteries, reported lowering the total cholesterol by 28.7%, 31% and 31% respectively. Also the LDL- cholesterol was lowered by 35.6%, 38% and 26% respectively. In the above mentioned studies the mean total cholesterol after the intervention was below 200 mg/dl and the LDL- cholesterol below 145 mg/dl. In my study the mean total cholesterol was 242 mg/dl and mean LDL-cholesterol was 163 mg/dl in the lifestyle group and total cholesterol was 231 mg/dl and LDL-cholesterol 153 mg/d in the medication group. The previous studies used both cholesterol lowering medication and lifestyle changes for a period of at least six months. The level of total cholesterol and LDL-cholesterol, rather than the percentage decrease, at the post-intervention reading may play an important role in the outcome. It could be that there is a lipid threshold at which the vascular endothelium function improves. Also, time may be a factor in the recovery of the vascular endothelium. Patients in my study may not have lowered their total cholesterol sufficiently to effect the impaired vasoreactivity. Another major difference between my study and those of Leung (1993), Egashira (1994)

and Treasure (1995), is that they all used the coronary arteries for the arterial measurements while I used the brachial artery. It could be that the effect of lowering cholesterol is evident sooner in the coronary arteries than in the brachial arteries, just as atherosclerosis is evident in the coronary arteries much sooner than any other arteries.

There were substantial differences between my study and the above referred to studies. The six week time period was chosen because cardiac patients attending aggressive lifestyle change programs such as Weimar Institute, Pritikin Longevity Center, etc, have reported a perceived significant improvement in their angina pectoris within 3-4 weeks of intervention, long before any significant reversal of coronary atherosclerotic plaque could be expected. It has also been reported in the literature that patients that are on cholesterol lowering therapy have a significant reduction of the angina pectoris symptoms within a few months of treatment in which time the regression of coronary atherosclerosis is unlikely to occur (Egashire et al, 1994; Brown et al, 1993; Ornish et al, 1990). Therefore the question is "is it possible that these people feel better because of the improvement on endothelial function due to the lower cholesterol?". Treasure et al (1995) have demonstrated that the endothelial improvement does not occur in 12 days after aggressive cholesterol lowering therapy. However he did see significant improvement in 5½ months (the total cholesterol and LDL cholesterol were the same at 12 days and 5½) which is consistant with Leung's and Egashira's findings. Therefore the time at which the endothelium improves it's function seems to be sometime after 12 days but prior to 6 months after intervention begun (see table 9). Further studies need to be done to test these possibilities.

Profile of Mood State

Institutions such as Weimar Institute (personal communication with Dr. Sang Lee), Pritikin Longevity Center and Wildwood Institute (personal communication with Dr. Geir Frivold), report that patients who participate in lifestyle change feel much better after three to four weeks of intervention at which time no angiographic improvement is evident. This study attempted to examine if there was any change in the mood status of the individuals who participated in lifestyle changes which could account to the health improvements that individuals report that they experience.

No significant changes were found in the mood state of individuals in any group in six weeks. The subjects met in a patient waiting room area prior to the ultrasound arterial measurements. The room was very small and some of the individuals had to stand in the corridor. It was during this time that the individuals filled out the POMS questionnaire, the stages of change questionnaire and the Nutritional Profile Plus. Thus the conditions may not have been ideal for answering the questions on feelings and thoughts. Also the conditions may not have been the same pre and post-intervention, since on some days there were several individuals to be tested and on other days there were very few.

However the results are consistent with reports from other studies (Blumenthall et al, 1988; Erdman et al, 1986; Dracup et al, 1991).

Table 9. Comparison Between Four Studies

Investigator	n	Time	Medication	Low fat diet	Pretest chol	Posttest chol	pretest LDL	Posttest LDL	Artery	Significance
Leung 1993	25	6 months	cholestyramin 8-16 g/day	yes	274	197	220	143	coronary	yes
Egashira 1994	9	6 months	pravastatin 10-20 mg/day	yes	272	187	195	120	coronary	yes
Treasure 1995	11	12 days	lovastatin 40-80 mg/day	yes	230	145	148	99	coronary	no
	11	5½ months	lovastatin 40-80 mg/day	yes	230	158	148	110	coronary	yes
Hardt 1996	17	6 weeks	none	yes	267	242	192	163	brachial	no
	17	6 weeks	pravastatin 20 mg/day	no	276	231	191	153	brachial	no

Stages of Change

From the four cluster K-means cluster analysis and the means of the URICA scale it is evident that the individuals in all groups scored the highest in the contemplation stage followed by the action stage. However the hypothesis that individuals who are in the action stage will be more successful in lowering their cholesterol than individuals that were not in action stage could not be tested. According to the literature only a small percentage of the population that need lifestyle changes are in the action stage assessed with URICA. For example only 7-15% of the smokers are in action stage (Abram et al, 1988; Pallonel et al, 1991; Gottlieb et al, 1990). No data was found for the percentage of individuals who are in action stage for lowering the cholesterol using the URICA. The sample size of my study may have been too small to find anyone that was in the action stage. The sample size was based on previous studies done on the effects of cholesterol on the EDRF. Since no statistical evaluations could be done on the few subjects who had high cholesterol levels and were in the action stage, there was no way to estimate the adequate number of individuals needed to participate. Ideally individuals should have been tested first to find out the stage of change they were in and then randomly assign equal numbers of each stage of change to each group. However this would have made the recruitment much difficult and time consuming. One interesting observation is that the subjects in the lifestyle group moved higher into the action stage at postintervention while the medication and placebo groups either dropped or remained the same. Individuals in the precontemplation stage are seeking information about the behavior they are considering changing and weighing the pros and cons of the change. The lifestyle group

evidently received enough information to increase their perception of the benefits of lowering the cholesterol and moved towards the action stage. It will be very interesting to follow these subjects up in six months and one year to see if they are more likely to maintain the changes they have made and if they are able to lower their cholesterol on their own as much as the medication group. Rossi et al (1990) found in a survey that 14.4% of the population are in the precontemplation stage as far as modifying their diet, 12.5% contemplators, 36.6% in action and 36.6% in maintenance. These results were taken by asking people if they are thinking to reduce their eating dietary fat, if they are ready to take an action in reducing their dietary fat intake to 30% or less, or if they already have done it. The URICA test was not used, and dietary intake was not taken, therefore I believe the results may not be accurate. However the National statistics indicate that only a small percentage of the U.S. population (7%) has actually achieved a fat consumption level less than 30% of the daily caloric intake (LSRO, 1989).

CHAPTER 6

SUMMARY AND CONCLUSIONS

Hypothesis Outcome

The hypothesis that lowering blood cholesterol levels by lifestyle or medication will reverse the abnormal EDRF response to vasodilating stimuli such as post occlusion hyperemia was not demonstrated by this study. However this may be due to the fact that the cholesterol levels did not decrease to the threshold level and the intervention time may have been too short. The present study has shown that lowering the cholesterol by lifestyle from a total cholesterol level of 267 mg/dl to 242 mg/dl or by medication from total cholesterol level of 276 mg/dl to 231 mg/dl in six weeks has no detectable effects on the brachial artery diameter. Further research is needed to examine the possibility of a lipid threshold at which the impaired endothelial function of the brachial artery recovers. Also further research is needed to establish the effect of time in the healing process of the arterial endothelium.

This study showed that total cholesterol and LDL-cholesterol can be lowered in outpatients through lifestyle intervention. Furthermore, it is possible to lower the total cholesterol and LDL-cholesterol without decreasing the HDL-cholesterol. An investigation needs to be done to identify the reason the HDL-cholesterol did not change.

No difference was found in the mood of individuals who lowered their cholesterol level by medication and those who lowered it by lifestyle changes in six weeks. However we cannot generalize that lowering the cholesterol by lifestyle or by medication has no effect on the mood, because this concept has not been tested over long periods of time. A

study following the lifestyle group and medication group for a longer time and testing periodically may be very helpful in testing this hypothesis.

The hypothesis that individuals in the action stage of change at the beginning of the intervention will be more likely to succeed in lowering their cholesterol level regardless of the group they were randomized into was not tested. The sample size was so small that none of the subjects were in the action stage of change at preintervention as assessed with the URICA. This research should be repeated with much larger sample size.

Strengths and Limitations

Even though high cholesterol is very prevalent in the United Sates of America, it was difficult to identify individuals who had high cholesterol levels but who had no other risk factors for atherosclerotic heart disease, such as hypertension, smoking and diabetes. Another factor that made it even more difficult to select the subjects was the widespread use of cholesterol lowering medications.

The participants were randomly assigned and there was no significant difference in the age, gender and weight distribution. A placebo group was used for comparison.

The lifestyle intervention lectures were well accepted by the participants. The low fat vegetarian food that was served to the lifestyle participants was well liked. The individuals expressed appreciation for the information they receive and for the food demonstrations.

Due to financial constrictions, personnel help was limited. The lifestyle group were free living and there was no way to monitor their activities at all times. There was

no control as to what they ate and how they exercise. The individuals participating in the lifestyle group were living at home. They were encouraged to participate in a regular exercise program on their own, and were purchasing and preparing their own meals with the exception of the two meals per week they were given during the intervention sessions. The majority of the participants were working and had to carry on their normal routine.

Due to financial restrictions the research design had to be cut short in time duration. Even though I would have liked to follow the participating individuals for a year repeating the blood lipid testing, brachial artery diameter measurements, stages of change assessment and moods determinations every six weeks finances would not allow it.

Because of the difficulties in recruiting individuals, some subjects had to wait 3-4 weeks from the time of their initial cholesterol, to the time the diameter of the brachial artery was measured. This may have caused some discrepancies in the pre-intervention data. Lack of finances made it impossible to repeat the lipid profile on the same day the brachial artery diameter was measured.

Because of the schedule of the echosonographer some subjects had to be tested several days after or before the due day. At times the echosonographer was unavailable and another person had to do the arterial testing. Also a timer was not used during the pre occlusion and post occlusion arterial measurements, therefore the time from the release of the tourniquet to the time of the actual reading of the measurements may not have been consistent.

According to the literature patients should have been prohibited from alcohol and

caffeine intake for at least 12 hours prior to testing (Creager et al, 1990). Dietary intake counseling for the day the arterial measurements were taken, was not given to the individuals. Neither was a dietary intake of that day taken.

The reliability of the acuson ultrasound image scanner was not checked, therefore reproducibility of the arterial measurements cannot be verified.

The patients' serum was not preserved and therefore replicate testing of the serum lipid profile was impossible. Having stored samples may have cleared up some questions that arose from reviewing the laboratory results if we had been able to retest the samples.

Recommendations

Methodological considerations. The appropriate funding should be available prior to starting the research. This will eliminate any shortcuts in time and procedures due to lack of finances, such as repeating a blood test. Appropriate personnel should be available to accomplish the tasks needed properly and timely. If any blood testing is a part of the research, I recommend that all serum samples be appropriately preserved till the end of the study.

Unanswered questions. there are some questions that are not answered in the literature or in the present study. These questions are:

1. Is there a lipid threshold at which the endothelial dysfunction occurs?
2. Is there a lipid threshold that the impaired endothelium will repair? and if so is it the same lipid threshold at which impairment occurs?
3. Does time after reaching the lipid threshold, if one exists, play a role in the impairment of the arterial endothelium?

4. What are the effects and the differences of lowering the cholesterol with medications and lifestyle over a long period of time?

5. Will individuals who are in the action stage be more successful in lowering and maintaining their cholesterol level than individuals in precontemplation and contemplation stage of change?

Recommendations. This research has generated concerns that should be addressed in a future research. A short and a long term study addressing the above questions should be considered.

Relevance to the Preventive Care Specialist

It is of a special interest to know that individuals can be successful in reducing their serum total cholesterol and LDL-cholesterol level, while maintaining the HDL-cholesterol, with lifestyle lectures and low fat food demonstration on an outpatient basis. The lectures included: nutritional information, stress management and exercise instructions. It is also encouraging to know that it is possible for individuals that reduce their fat intake, adapt an exercise program and learn how to manage stress to reduce both the systolic and diastolic blood pressure.

It is of a special interest to a preventive care specialist to know that the mood of the individuals that have made lifestyle changes may not change significantly in six weeks. There is no difference in the mood of the individuals that lower their serum cholesterol level with lifestyle changes and the ones that lower their serum cholesterol level with medication in six weeks.

Treatment of cholesterol with lifestyle changes has some advantages over

cholesterol lowering drug therapy. Even though cholesterol lowering drugs are very effective in lowering the total cholesterol and LDL cholesterol, they have several adverse effect (PDR, 1995). The cost of cholesterol medication varies from 1,000 to 3,000 dollars per year. Lifestyle intervention has no adverse effects and it is cost effective (Bly et al, 1986; Gebhardt & Crump, 1990; Bertera, 1990; Pelletie, 1991; Oldenburg et al, 1995). However the current methods of nonpharmacological approach have been somewhat disappointing. Interventions aimed at changing lifestyle risk factors such as diet have report less than 50% adherence to the regimen (Rossi et al, 1990). Failure to match dietary programs with individual's readiness to change is implicated as major reason for poor adherence rates (Rossi et al, 1990). Programs can be developed that are specifically geared to individuals who are in precontemplation stage to move them to contemplation, and the ones that are in contemplation to action. When individuals are at the action stage, the programs can be geared to the particular behavior change and to move the individuals to the maintenance stage. In this study the lifestyle group increased in action stage in the six week intervention.

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LIST OF APPENDICES

APPENDIX A-1

LIFESTYLE LECTURE # 1

1. Definition of desirable, borderline and high serum lipid values.

2. Effects of high serum cholesterol levels on health.

3. Food guide pyramid: a guide to daily food choices.

4. Recommended diet : 15% fat, mostly monounsaturated (olive oil & canola oil)
   10-15% protein
   70 % carbohydrates (complex)

5. Nutritional facts. How to read the nutritional facts on the food labels.
   Explanation of grams and calories

6. Exercise: Types of exercise (aerobic, strength & flexibility)
   Benefits of each type of exercise
   Aerobic exercise frequency, intensity, duration & progression.

7. Stress management: Definition of eustress and distress
   Identification of stressors
   Stress test.

8. Food served: Pita bread sandwich with vegetarian refried beans.
   Tomatoes, lettuce and salsa
   Carrots
   Apples
   Apple juice

9. Calculation of total calories and macro-nutrients in the meal.

Handouts: Food guide pyramid
Protective factors of low fat diet
Small steps can make a big fat difference
Exercise benefits and Eight exercise tips
Exercise program &Target heart rate
Stress test
Low fat recipes

APPENDIX A-2

LIFESTYLE LECTURE # 2

1. Review of lifestyle lecture # 1

2. Discussion of the changes each participant made after the lifestyle lecture 1.

3. Discussion on the Nutritional Profile Plus results.

4. Protective factors for heart disease.

5. Food exchange list.

6. Eating triggers.

7. Signs of stress.

8. Stress coping strategies. Deep breathing
   Time management

9. Food served: Pea stew
   Whole wheat bread roles with jam
   Low fat oatmeal cookies
   Diet soda.

9. Calculation of total calories and macro-nutrients in the meal.

Handouts: Eating triggers
Calorie controlled diet booklet (complements of Kaiser Permanente Medical Care Program)
Low fat recipes

APPENDIX A-3

LIFESTYLE LECTURE # 3

1. Review lifestyle lectures #1 & 2.

2. Discussion of the changes each participant made after the lifestyle lecture # 2.

3. Successful menu planning.

3. 30 minute Video on exercise.

4. Discussion on exercise and health benefits.

5. Food served: Low fat noodle casserole
   Salad with seasoned rice vinegar
   Carrots
   Fat free ice cream

6. Calculations of total calories and macro-nutrients in the meal.

Handouts: Successful meal planning
   Meal patterns
   Low fat recipes

APPENDIX A-4

LIFESTYLE LECTURE # 4

1. Review of lifestyle lectures # 2 & 3.

2. Discussion of the changes the participants made.

3. Hassles and uplifts scale.

4. Fiber facts.

5. Eating out.

6. Substitutions for fat in cooking.

7. Food served: Mediterranean soup
   Whole wheat bread
   Fat free cream cheese & jam
   Fruit (apples and grapes)

8. Calculation of total calories and macro-nutrients in the meal.

Handouts: Hassles and uplifts scale
Where is fiver found
Substitutes for fat
Low fat recipes

APPENDIX A-5

LIFESTYLE LECTURE # 5

1. Review of lifestyle lectures # 1-4.

2. Discussion of each individuals progress.

3. Stress management techniques: deep breathing
   progressive muscle relaxation

4. Food served: Brown rice-kidney bean-carbanzo casserole
   Steamed broccoli
   Steamed carrots
   Salad with fat free ranch salad dressing
   Watermelon

5. Calculation of total calories and macro-nutrients in the meal.

APPENDIX A-6

LIFESTYLE LECTURE # 6

1. Stress and Strains Vedeo.

2. Joharis window of life

3. Unconscious-conscious habits.

4. Talked about the different exercises each individual was participating in.

5. Food served: Chilli beans
   Whole wheat saltine crackers
   Whole wheat bread
   Sliced tomatoes
   Baby carrots
   Blueberry supreme cake

7. Calculation of total calories and macro-nutrients in the meal.

APPENDIX A-7

LIFESTYLE LECTURE # 7

1. Review of lifestyle lecture # 6.

2. Mid-program personal assessment.

3.. The digestion of food.

4. Exercise program review

5. Food served: Low fat spinach lasagna
   Cruciferous vegetables saute.
   Salad with olive oil, lemon and salt
   Bread with fat free margarine and jam
   Fruit (honey due and cantaloupe)

6. Calculations of the total calories and macro-nutrients in the meal.

7. Handouts: low fat recipes.

APPENDIX A-8

LIFESTYLE LECTURE # 8

1. Review of lifestyle lecture # 7.

2. Discussion on each individuals progress and concerns.

3. Effect of caffeine on the body and specifically on the cholesterol.

4. Stress management exercise: letting go.

5. Food served: Lentils on rice
   Salad
   Salsa
   Apple juice
   Fat free ice cream and fat free cookies

6. Calculation of total calories and macro nutrients in the food.

Handouts: Answers to some caffeine questions
Poem on letting go
Low fat recipes

APPENDIX A-9

LIFESTYLE LECTURE # 9

1. Review of lifestyle lecture # 8.

2. Discussion on each individuals progress.

3. Stress management and personal strength inventory.

4. Personality type and stress.

5. Food served: Lentils
   Whole wheat bread
   Salad
   Picante salsa
   Fruit (grapes, apples, bananas)

6. Calculation of total calories and macro-nutrients in the meal.

APPENDIX A-10

LIFESTYLE LECTURE #10

1. Review of lifestyle lecture #9.

2. Discussion on each individuals progress.

3. Suggestions on eating out.

4. Exercise program review.

5. Relapse prevention.

6. Food served: Baked potatoes
   Fat free mushroom gravy
   Steamed zucchini
   Saute kale
   Non-fat cherry cheese cake

7. Calculation of total calories and macro-nutrient in the meal.

Handouts: Fast foods highest in fat
Fast foods lowest in fat
Low fat recipes

APPENDIX A-11

LIFESTYLE LECTURE #11

1. Review of lifestyle lecture # 11.

2. Discussion on each individuals progress.

3. Phytocemicals.

4. Stress management and distorted thinking

5. Food served: Brown rice
   Black beans
   Salad
   Fat free salad dressing
   Corn
   Whole wheat bread roles with jam
   Fruit (melons)

6. Calculation of calories and macro-nutrients in the meal.

Handouts: List of phytochemicals in vegetables and fruits.

APPENDIX A-12

LIFESTYLE LECTURE # 12

1. Review of lifestyle lecture #11.

2. Class evaluation.

3. Meal served: falafel sandwiches
   Broiled vegetables (red potatoes, yams, zucchini, onion halves, eggplant)
   Apple crisp
   Fat free ice cream

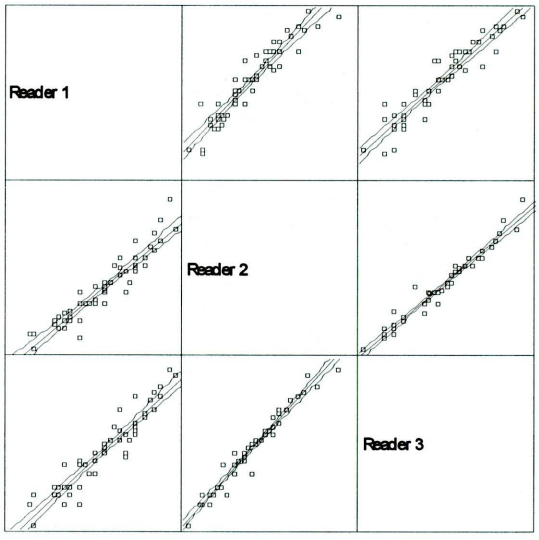
4. Calculation of total calories and macro-nutrients in the meal.

APPENDIX B-1

Scatterplot of Interrater Agreement Pretest Preocclusion and Postocclusion Longitudinal Brachial Artery Diameter

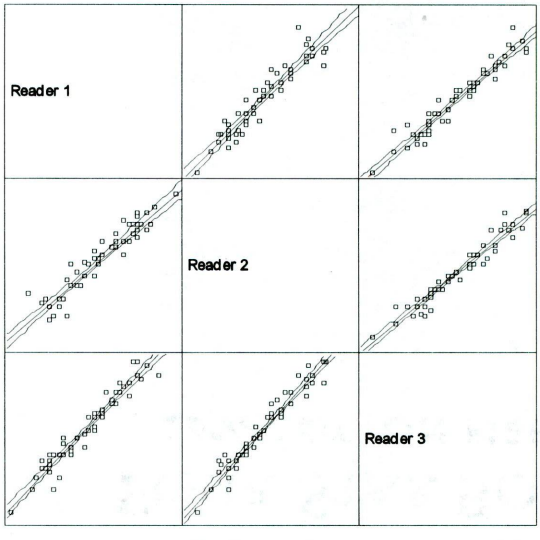
Pretest Preocclusion

Longitudinal Brachial Artery Diameter



Pretest Postocclusion

Longitudinal Brachial Artery Diameter

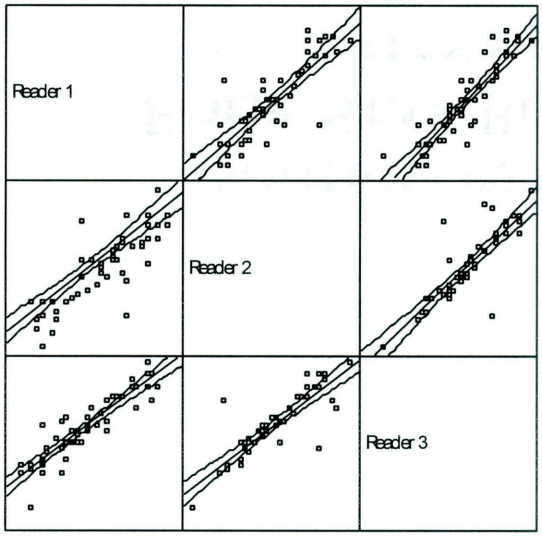


APPENDIX B-2

Scatterplot of Interrater Agreement Posttest Preocclusion and Postocclusion Longitudinal Brachial Artery Diameter

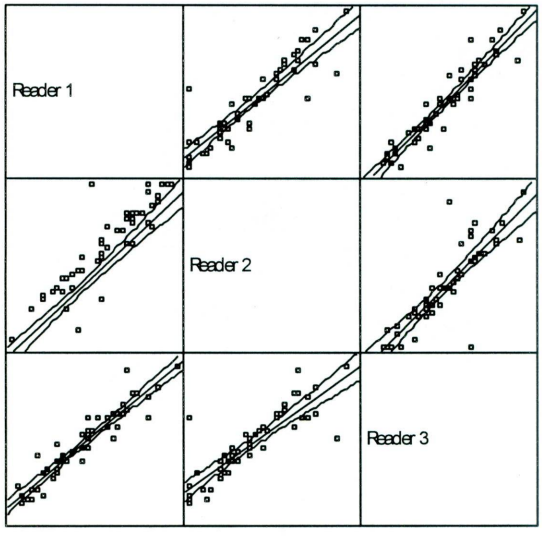
Posttest Preocclusion

Longitudinal Brachial Artery Diameter



Posttest Postocclusion

Longitudinal Brachial Artery Diameter

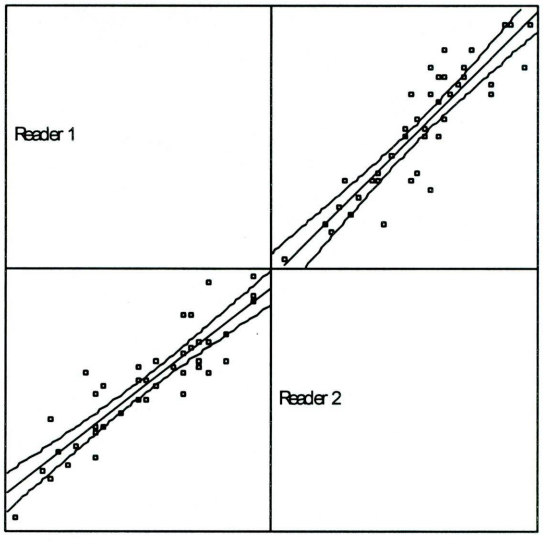


APPENDIX B-3

Scatterplot of Interrater Agreement Pretest Preocclusion and Postocclusion Transverse Brachial Artery Diameter

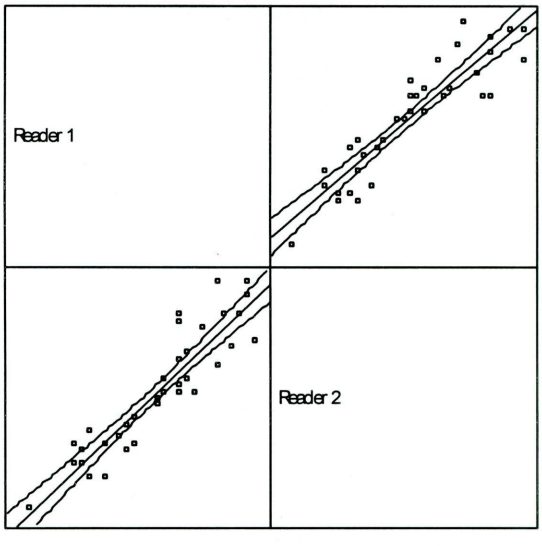
Pretest Preocclusion

Transverse Brachial Artery Diameter



Pretest Postocclusion

Transverse Brachial Artery Diameter

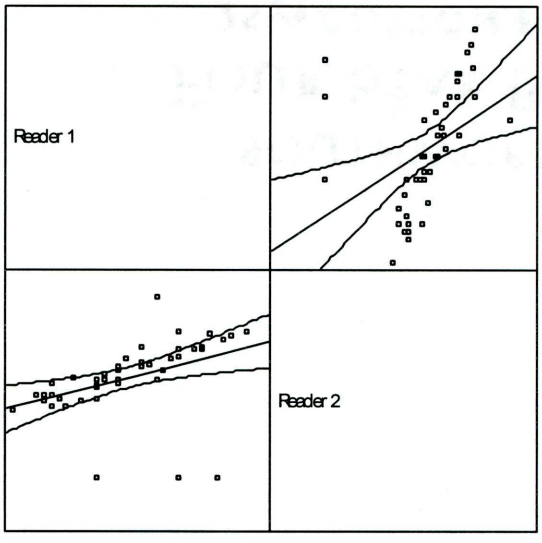


APPENDIX B-4

Scatterplot of Interrater Agreement Posttest Preocclusion and Postocclusion Transverse Brachial Artery Diameter

Posttest Preocclusion

Transverse Brachial Artery Diameter



Posttest Postocclusion

Transverse Brachial Artery Diameter